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Inhibition of Myometrial Activity
During Human Pregnancy
by β -adrenoceptor Stimulation

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INHIBITION OF MYOMETRIAL ACTIVITY DURING HUMAN
PREGNANCY BY β -ADRENOCEPTOR STIMULATION

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INHIBITION OF MYOMETRIAL ACTIVITY DURING HUMAN
PREGNANCY BY β -ADRENOCEPTOR STIMULATION

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The present thesis is based on the following papers

- I Andersson, K.-E., Ingemarsson, I., and Persson, C.G.A.: Relaxing effects of β -receptor stimulators in isolated, gravid human myometrium. *Life Sci.* 13: 335, 1973.
- II Andersson, K.-E., Ingemarsson, I., and Persson, C.G.A.: Effects of terbutaline on human uterine motility at term. *Acta Obstet. Gynecol. Scand.* 54: 165, 1975.
- III Andersson, K.-E., Bengtsson, L.Ph., Gustafson, I., and Ingemarsson, I.: The relaxing effect of terbutaline on the human uterus during term labour. *Am. J. Obstet. Gynecol.* 121: 602, 1975.
- IV Andersson, K.-E., Bengtsson, L.Ph., and Ingemarsson, I.: Terbutaline inhibition of midtrimester uterine activity induced by prostaglandin $F_{2\alpha}$ and hypertonic saline. Accepted for publication in *J. Obstet. Gynaecol. Br. Commonw.*
- V Ingemarsson, I.: Effect of terbutaline on premature labour - a double-blind placebo-controlled study. Submitted for publication in *Am. J. Obstet. Gynecol.*

In the text the papers are referred to by their Roman numerals.

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1. INTRODUCTION

For years, the effects of sympathomimetics on different organs and in different species have been investigated. Langley (1905) provided the basis of current concepts of adrenergic receptors, suggesting that effector cells contain both excitatory and inhibitory "substances", and that the response to adrenaline is dependent upon which type of "substance" is predominant in a particular structure. Dale (1906) was the first to use the receptor concept when comparing effects of sympathetic nerve-stimulation and stimulation with adrenaline. He suggested that the sympathetic neuromuscular junction was the "receptive mechanism for adrenaline". The blocking actions of ergot alkaloids were studied from that aspect. He also showed that the responses of cat uterus to sympathetic stimulation varied with the hormonal condition.

Ahlquist (1948) introduced the currently employed nomenclature. The effects of different agonists were compared in order to characterize the adrenergic receptor biologically. He concluded that there are two distinct types of adrenergic receptors (adrenoceptors): α and β . The differentiation of these receptors was based on the rank order of potency in various organs of 5 sympathomimetic amines. Stimulation of the α -adrenoceptors was associated with excitatory responses, except for inhibition of the gastrointestinal tract; stimulation of the β -adrenoceptors was associated with inhibitory responses, except for cardiac stimulation.

With the introduction of β -receptor blockers, dichloroisoproterenol and propranolol, the β -receptors could be investigated more specifically (Powell and Slater, 1958, Black et al., 1964).

The concept of the adrenergic receptors has been further evaluated by Lands et al. (1967), who proposed that the β -receptors can be differentiated into two sub-types, β_1 and β_2 . Adrenergic

receptors of the β_2 -type are predominant in, for instance, uterus, vascular smooth muscle, and bronchial smooth muscle, whereas the heart contains receptors of β_1 -type. Today, there are drugs with stimulating and blocking actions mainly on β_1 - and β_2 -receptors.

However, the uterus seems to offer a great challenge to the researcher into the adrenergic pharmacology. Antipodal responses have been obtained on the same apparent stimulus in different species and also in the same species under different hormonal conditions (for review, see Pauerstein and Zander, 1970). Some of these conflicting results might be explained by the adrenergic neurotransmitters possessing both α - and β -receptor stimulating properties. The uterine activity of most species seems to be under adrenergic control by a balance between α - and β -activity (Ahlquist, 1966).

Adrenaline, stimulating both α - and β -receptors, can therefore both increase and diminish the uterine activity. In humans, the drug stimulates the activity of the nonpregnant and pregnant uterus in vitro (Stander and Barden, 1966, Nakanishi et al., 1969), but in vivo, the pregnant uterus responds mainly with relaxation (Rucker, 1925, Garret, 1959). Pose et al. (1962) demonstrated inhibitory effects of adrenaline on the uterine activity at term, but observed, after discontinuation of the infusion, a "rebound" effect with increased uterine activity and elevated tone. Because of this and of the adverse effects on the maternal circulation, adrenaline is unsuitable for obstetric use.

In order to inhibit the uterine activity, drugs with effects mainly on the β -receptors of the uterus should be preferable. Konzett (1940) introduced isoprenaline, which was shown to act almost exclusively on the β -receptors. Infusion of isoprenaline produced inhibition of uterine activity at term (Mahon et al., 1967), but pronounced cardioacceleration and hypotension prevented its clinical use.

Isoxsuprine was the first drug suitable for clinical depression of uterine activity in pregnancy (Brücke et al., 1956). It mainly affects the β -receptors (Lish et al., 1960) although other mechanisms can be of importance (Landesman and Wilson, 1968). Several investigations have demonstrated this drug's ability to inhibit uterine activity both in premature labour (Bishop and Wouterz, 1961, Hendricks, 1964, Allen et al., 1965) and at term (Hendricks et al., 1961, Stander et al., 1964). It has been used for several years for inhibiting unwanted uterine activity and is still recommended (Zuspan et al., 1972). However, side effects of the maternal circulation, tachycardia, and hypotension, limit its clinical usefulness.

According to Ahlquist (1948), bronchial and uterine smooth muscle contain β -receptors; later classified as β_2 -type. Sympathomimetic bronchodilator drugs should therefore be effective also as myometrial relaxants. Orciprenaline has been shown to be a potent inhibitor of uterine activity both in premature labour (Baillie et al., 1970) and at term (Eskes et al., 1966, Tyack et al., 1971, Melander and Lindmark, 1972). However, pronounced maternal tachycardia and also cardiac arrhythmias during infusion treatment have been reported (Zilianti and Aller, 1971).

Drugs with stimulating effects mainly on the β_2 -receptors, for instance, salbutamol, terbutaline, and fenoterol have recently become available. They have been extensively used as bronchodilators. Several investigations have demonstrated that, for obstetric use, salbutamol (Liggins and Vaughan, 1973, Korda et al., 1974) and fenoterol (Maiss and Legerlotz, 1972, Schmidt and Hirdes, 1973) are suitable for inhibition of uterine activity both in premature labour and at term. A moderate maternal tachycardia has been observed during infusion treatment, but the blood pressure has been very little affected, except for a slight increase in pulse pressure.

Ritodrine was synthesized mainly for obstetric indications and

is well investigated. It is said to be a "selective" β_2 -receptor stimulator with potent inhibitory effects on uterine activity in premature labour and at term (Baumgarten et al., 1971, Landesman et al., 1971, Barden, 1972, Bienarz et al., 1972, Fröhlich, 1973, Renaud et al., 1974). The side effects during treatment with ritodrine seem to be similar to those of fenoterol and salbutamol.

Terbutaline, a β -receptor stimulator with effects mainly on β_2 -receptors (Persson and Olsson, 1970, Olsson and Persson, 1971, Engelhardt and Traunecker, 1972) is clinically a potent bronchodilator (Arner et al., 1970, Freedman, 1972, Dulfano and Glass, 1973). According to the experiences related above, it might be a drug suitable for obstetric use. In the present study, therefore, the effects of terbutaline on myometrial activity during pregnancy were investigated. The aims of the investigations were:

1. To characterize the β -receptor of the human uterus by studying in vitro the effects of α - and β -receptor stimulators and the corresponding blockers in normally polarized and in depolarized muscle strips from human myometrium obtained at caesarean sections at term (Papers I and II).
2. To correlate the in vitro findings with studies in vivo during labour at term by using the β_2 -receptor stimulator terbutaline, the non-selective β -receptor blocker propranolol, and the selective β_1 -receptor blocker practolol (Paper II).
3. To evaluate in vivo the effects of terbutaline on uterine activity and cardiovascular system of the mother and the fetal heart rate during labour at term (Paper III).
4. To study in vivo the effects of terbutaline on uterine activity in mid-pregnancy induced by $\text{PGF}_{2\alpha}$ and hypertonic saline (Paper IV).
5. To evaluate the effect of terbutaline in premature labour (Paper V).

2. MATERIAL AND METHODS

A. In vitro. Seventy-two preparations from 20 patients were dissected from strips taken from the lower uterine segment at caesarean sections performed at term. 2 – 4 strips from each muscle piece were mounted in an organ bath filled with Krebs solution and were run simultaneously; one or two of them served as controls. For details of the experiments, see Papers I and II.

Spontaneous contractile activity with a regular pattern could be demonstrated in all preparations after a period of stabilization. Thirty of the strips (Paper I) were depolarized by exchanging the sodium of the Krebs medium by an equivalent amount of potassium. The drugs were injected directly into the bath.

B. In vivo. An extra-amniotic technique was used for continuously recording the intra-uterine pressure at term. A sponge-tipped open end catheter (Bengtsson, 1968) was inserted through the cervical canal and placed between the uterine wall and the membranes. The catheter was connected to a pressure transducer (Hewlett Packard, model 8020 A). Fifteen patients with intact membranes were studied during spontaneous or oxytocin-induced labour. In 9 of them, the cervix was effaced and dilated 4 – 5 cm (Papers II and III). Four patients were in advanced labour with the cervix dilated at least 8 cm and two were in the second stage of labour (Paper III).

One patient developing clinical signs of uterine hyperactivity in connexion with oxytocin-stimulation was studied in the same way. In another patient, where fetal bradycardia developed during oxytocin-stimulation, the contractions were registered by external tocography (Paper III).

A percutaneous technique was used for recording the uterine activity in mid-pregnancy (Paper IV). Twenty patients (16th to 20th week of pregnancy) undergoing therapeutic abortion induced

by hypertonic saline (10 patients) or prostaglandin $F_{2\alpha}$ (10 patients) were investigated. After transabdominal puncture of the uterine cavity, 100 ml of amniotic fluid was withdrawn in the patients receiving hypertonic saline and then 20 per cent NaCl-solution was instilled (10 ml per week of pregnancy). In the patients given prostaglandin $F_{2\alpha}$, 25 mg of the drug was injected into the amniotic cavity without withdrawal of fluid. After this procedure, a catheter for epidural anaesthesia (Portex 100/380/20, open end with side holes) was introduced into the cavity and attached to the same type of transducer as above.

The uterine activity, both in mid-pregnancy and at term, was recorded on a cardiotocograph (Hewlett Packard 1280 B). With the same apparatus, the fetal heart rate at term was registered by means of an ultrasonic flow detector; the detector was used to record the maternal heart rate in the abortion patients.

The maternal blood pressure was followed continuously in 9 patients at term (Papers II and III) through a polyethylene catheter (Stille Werner, Sweden) inserted into the radial artery and was monitored on an ink-jet recorder (Mingograph 81, Elema Schönander, Sweden) via a pressure transducer (EMT, 746, Elema Schönander, Sweden).

Infusions were given by an infusion pump (IVAC 501, AGA, Sweden) through catheters inserted into forearm veins.

Patients with premature labour of unknown aetiology were studied (Paper V). Those with toxæmia, uterine malformations, fever, twins, or vaginal bleeding were excluded. The selected patients fulfilled the following criteria:

1. Duration of gestation 28 – 36 weeks
2. Intact membranes
3. Painful, regular uterine contractions, occurring at intervals of less than 10 minutes, recorded for at least 30 min by external tocography.

4. The cervix effaced or almost effaced, dilated at least 1 – 2 cm, but not more than 4 cm.

All patients were examined by the same investigator. External tocography was used to record the uterine contractions (Hewlett Packard 1280 B), the fetal heart rate being monitored on the cardiocotocograph with an ultrasonic flow detector (Hewlett Packard).

The effect of terbutaline was compared with that of placebo in 30 patients, 15 in the terbutaline group and 15 in the placebo group. The two groups were statistically comparable. All patients were treated with bed rest and sedatives; in addition, terbutaline or placebo were allocated at random. The two groups were treated in a double-blind manner. Treatment consisted of an intravenous infusion for at least 8 hours (terbutaline or placebo = physiological saline). After the infusion, the patients were given subcutaneous injections (corresponding to 250 µg of terbutaline) 4 times daily for 3 days together with peroral treatment (corresponding to 5 mg x 3 of terbutaline) which was continued until the end of the 36th week of pregnancy. For details of the treatment scheme, see Paper V.

Patients with delivery postponed until the 37th week of gestation or later were considered successfully treated; others, failures.

3. RESULTS

A. In vitro, depolarized muscle

After depolarization with potassium, the uterine strips rapidly developed a phasic contracture, followed by a second, slowly developing increase in tension to a steady state level. The studies were performed when a stable tension level had been achieved. The baseline tension was between 200 and 600 mg. The strip responded with relaxation to isoprenaline (0.004 – 0.4 $\mu\text{g/ml}$) or terbutaline (0.008 – 8 $\mu\text{g/ml}$). This relaxation could be blocked by propranolol (0.1 $\mu\text{g/ml}$). The effect of the two amines was not affected by phenoxybenzamine (0.1 – 1 $\mu\text{g/ml}$) but this drug was able to block the stimulatory responses of noradrenaline (0.1 – 1.2 $\mu\text{g/ml}$). Neither propranolol nor phenoxybenzamine by itself affected the tension level of the strips.

B. In vitro, normally polarized muscle

The effects of drugs on the spontaneous contractile activity of normally polarized myometrial strips were studied. Isoprenaline (0.02 – 0.4 $\mu\text{g/ml}$) and terbutaline (0.2 – 8 $\mu\text{g/ml}$) diminished both the frequency and the amplitude of the contractions; in many strips, the activity was abolished. In contrast, noradrenaline and adrenaline (0.1 – 0.4 $\mu\text{g/ml}$) increased the spontaneous contractile activity, but this effect was blocked when phenoxybenzamine (0.1 – 0.5 $\mu\text{g/ml}$) was added to the bath. If the strip was pre-treated with phenoxybenzamine, noradrenaline and adrenaline caused inhibition. Phenoxybenzamine by itself had no effect on the spontaneous activity and could not affect the inhibitory responses of isoprenaline and terbutaline.

Propranolol (blocking both β_1 - and β_2 -receptors) and practolol and H93/26 (affecting mainly β_1 -receptors) were also studied. In a concentration of 1 $\mu\text{g/ml}$, the two β_1 -receptor blockers could not prevent the inhibition produced by isoprenaline and terbutaline.

However, in concentrations of 5 and 10 $\mu\text{g/ml}$, practolol and H93/26 reduced, but never abolished, the inhibitory effects on the β -receptor stimulators. By themselves, the two blockers had no effect on the spontaneous contractile activity of the strips. On the other hand, propranolol completely blocked the effects of isoprenaline and terbutaline. Propranolol by itself did not affect the activity of the muscle strips, except in one preparation.

C. In vivo, term

The effect of terbutaline was studied in 15 patients in term labour (Papers II and III). Infusion of terbutaline (10 – 20 $\mu\text{g/min}$) during 20 – 45 minutes effectively inhibited spontaneous and also oxytocin-induced labour. The effect was more pronounced on the intensity of the contractions than on the frequency. The effect appeared within a few minutes and seemed to be similar regardless of the stage of labour. Thus, inhibition of the uterine activity could be demonstrated in the second stage of labour as well as in the first stage when the cervix was dilated 4 – 5 cm. Oxytocin-induced hyperactivity of the uterus and fetal bradycardia induced by oxytocin stimulation were successfully treated by terbutaline, 250 μg intravenously.

The effects of propranolol and practolol were compared with the findings in isolated uterine tissue in 6 of the patients. When the uterus was relaxed by infusion of terbutaline, the activity returned promptly to the pre-infusion level after an intravenous injection of propranolol (1 – 2 mg). Pre-treatment with propranolol made the uterus unresponsive to β -receptor stimulation with terbutaline. In contrast, practolol (5 – 20 mg intravenously) did not affect the inhibitory effect of terbutaline. These results agree well with the effects of terbutaline and β -receptor blockers on isolated myometrial strips.

The changes in maternal blood pressure during infusion of terbutaline were small. There was a minor increase in pulse

pressure, but the mean blood pressure was practically unchanged. All patients had an increase in the heart rate, which persisted for a variable period after the end of infusion. In 9 patients, where intra-arterial registration was performed, a mean maximum increase from 80 to 119 beats per minute was recorded. Propranolol prevented this tachycardia if given before the terbutaline infusion. If injected during or immediately after infusion of terbutaline, propranolol reduced the heart rate to pre-infusion values. In the few patients receiving practolol, no effect could be demonstrated on the maternal heart rate.

In most cases, a small to moderate increase in fetal heart rate was recorded during terbutaline infusion, but the heart rate of the fetus never exceeded 160 beats per minute.

D. In vivo, mid-pregnancy

The effect of terbutaline on uterine activity, induced by $\text{PGF}_{2\alpha}$ and hypertonic saline, was investigated. The drug was infused at an increasing rate from 5 $\mu\text{g}/\text{min}$ to 20 $\mu\text{g}/\text{min}$ (total dose 500 μg given during 40 minutes). During infusion of terbutaline, the uterine activity, expressed in Montevideo Units, decreased by approximately the same amount. The pre-infusion values were higher in the prostaglandin group (mean 393 Montevideo Units) than in the hypertonic saline group (mean 238 Montevideo Units). This difference depended mainly on a higher frequency of contractions in the prostaglandin group, as the intensity was similar in the two groups. Terbutaline infusion decreased both the frequency and the intensity of the contractions in the hypertonic saline group (in two patients the activity was completely inhibited). The decrease in uterine activity in the prostaglandin group depended mostly on a decrease in frequency of the contractions, as the intensity was little affected.

The basal tone was more reduced in the prostaglandin group than in the hypertonic saline group, where the level was low

before the infusion of terbutaline.

The effects of terbutaline infusion on maternal blood pressure and heart rate were similar to the alternations described above during term labour. For recording details and abortion procedure, see Paper IV.

E. Premature labour

The premature labour was arrested beyond the treatment period in 12 of 15 (80 per cent) of the patients receiving terbutaline. Seven of them were delivered in the 37 - 38th week; the rest at term. In 3 patients, the treatment failed. Two of them had a quite advanced cervical status (3 cm dilated); the third showed signs of abruptio placenta during infusion treatment, which is why this was stopped. In the placebo group, 10 patients were delivered within 24 hours from the start of infusion. In two patients, the delivery could be postponed for 3 and 14 days, respectively. The premature labour was arrested beyond the treatment period (36th week) in only 3 patients of 15 (20 per cent). The difference in results of treatment between the placebo and terbutaline groups is statistically significant ($p < 0.01$).

The Apgar score at delivery was uniformly good, and there was in this material no perinatal or neonatal deaths among the children. In the terbutaline group, 4 children weighed less than 2,500 g (mean birth weight for the group 3,060 g) compared with 10 children in the placebo group (mean birth weight for the group 2,190 g).

No serious side effects of the therapy were observed. Maternal tachycardia during infusions was more pronounced in the terbutaline group (mean increase 30 per cent) than in the placebo group (mean increase 9 per cent). Hypotension occurred once in the terbutaline group and twice in the placebo group, but it was symptomless and was easy to correct. Fetal tachycardia (≥ 150 beats/min) was more often recorded in the terbutaline

group (80 per cent) than in the placebo group (30 per cent), but it never exceeded 175 beats/min.

Side effects of the therapy were well tolerated by the patients and did not lead to any discontinuance of treatment.

4. GENERAL DISCUSSION

Conflicting results have been reported about the effects of β -receptor stimulators on isolated human myometrium. Isoprenaline was demonstrated to inhibit spontaneous activity in human myometrium in vitro (Stander and Barden, 1966, Landesman and Wilson, 1968) but some investigators have reported weak or no inhibitory effect of this amine or even a stimulatory action (Lehrer, 1965, Grün et al., 1971). Sullivan and Marshall (1970) found relaxing effects of isoprenaline in normally polarized, but not in depolarized, human myometrium. Noradrenaline and adrenaline produced excitatory responses in both polarized and depolarized preparations. They therefore concluded that a normal membrane potential is necessary for the relaxing effects of isoprenaline. However, the present studies showed that isoprenaline and also terbutaline in low concentrations were able to relax both normally polarized and depolarized human uterine muscle. It was also shown that the inhibitory effects of isoprenaline and terbutaline were blocked by the non-selective β -receptor blocker propranolol and that the α -receptor blocker phenoxybenzamine had no effect on the actions of the two amines. These results suggest that the effects were mediated via β -receptors. When the α -receptors were blocked by phenoxybenzamine, the stimulatory effects of noradrenaline and adrenaline were reversed into inhibition, a finding that supports this presumption.

Animal investigations proved that isoprenaline was about 20 times more active than terbutaline on the β -receptors of the lung and 500 times more active than terbutaline on the β -receptors of the heart (Persson and Olsson, 1970). The potency ratio between the two amines that could be demonstrated on human myometrium suggests that the relaxation produced by isoprenaline and terbutaline are mediated by β_2 -receptors. Further evidence was achieved by investigating the effects of the selective β_1 -blockers practolol

and H93/26. These blockers did not affect the inhibitory responses of isoprenaline and terbutaline, except in high concentrations. Thus, from these results, it could be concluded that the effects of isoprenaline and terbutaline on the human myometrium are mediated by actions on β -adrenoceptors, probably of β_2 -type.

These findings in vitro could be correlated with the results obtained in vivo. Terbutaline was shown to effectively inhibit uterine activity at term, both spontaneous and oxytocin-induced. Most of the patients had a strong uterine activity: the mean intensity of the contractions exceeded 50 mm Hg. The relaxing effect was practically immediate and independent of the stage of labour. The inhibitory effects of terbutaline were not affected by the β_1 -blocker practolol, but were blocked by propranolol. The demonstrated effects of propranolol, given intravenously, suggest the suitability of this drug as an antidote should adverse side effects of terbutaline arise.

The side effects of terbutaline treatment were moderate and well tolerated by the patients during infusions of short duration and also during intensive infusion therapy in premature labour. No hypotension of clinical importance was recorded, in contrast to reported observations during treatment with non-selective β -receptor stimulators such as isoprenaline and isoxsuprine (Stander et al., 1964, Mahon et al., 1967). Maternal tachycardia was seen in every patient during infusion therapy with terbutaline, but it did not seem to be of a degree that could seriously interfere with the clinical usefulness.

Long infusion times and repeated infusions are often necessary in premature labour therapy. Terbutaline seems to be suitable for this type of intensive therapy. A comparison with other selective β_2 -receptor stimulators concerning the side effects is difficult, as differences exist in treatment schemes, infusion rates, and times of infusion in reported investigations. None the less, the reported side effects of these drugs on the maternal circulation

(Liggins and Vaughan, 1973, Schmidt and Hirdes, 1973, Bienarz et al., 1974) seem to be qualitatively and quantitatively similar to those of terbutaline.

An important question is whether β -receptor stimulators are effective for inhibition of induced uterine activity. Oxytocin-induced labour at term was in this study shown to be inhibited to the same degree as spontaneous activity. The effects of β -receptor stimulation on uterine activity induced by another important stimulator, prostaglandin $F_{2\alpha}$, have been studied in only few investigations. Lindmark et al. (1973) found that orciprenaline and ritodrine reduced uterine activity induced by $PGF_{2\alpha}$ in women undergoing therapeutic abortion in the second trimester. Orciprenaline has also been shown to inhibit uterine activity at term induced by $PGF_{2\alpha}$ given intravenously (Baillie and Jonathan, 1972, Scher and Baillie, 1972).

According to a hypothesis introduced by Gustavii (1973), prostaglandins, at least to some extent, are responsible for the uterine activity induced by hypertonic saline, which is believed to act via synthesis and release of prostaglandins from damaged decidual cells. We therefore found it of interest to compare the effect of terbutaline on uterine activity induced by intra-amniotically administered hypertonic saline and prostaglandin $F_{2\alpha}$ in second trimester abortions. Terbutaline was shown to reduce the uterine activity in all patients. The degree of inhibition, expressed in Montevideo Units, was of the same order for both prostaglandin and hypertonic saline-induced activity, although the pre-treatment values of uterine activity were higher in the prostaglandin group. It is notable that the inhibition produced by terbutaline under these circumstances was much less pronounced than its effect during term labour.

Premature labour is a great problem in obstetric practice. Many drugs have been tested for treating premature labour with varying degrees of success (for review, see Zuspan et al., 1972). The

selective β -receptor stimulators available today allows a more intensive therapy to be performed, as the side effects are well tolerated. New drugs of this type, for instance, ritodrine, fenoterol, and salbutamol, have been investigated in premature labour, and promising results have been reported. Unfortunately, only a few of these studies have been adequately controlled. This has restricted the value of the reported results, because the diagnosis premature labour is difficult to establish and the effect of conservative treatment, for instance, bed rest and sedatives, is unknown. However, in controlled studies, ritodrine has been shown to significantly prolong the pregnancy in premature labour (Wesselius-de Casparis et al., 1971, Sivasamboo, 1973).

Terbutaline was investigated in a double-blind placebo-controlled study in 30 patients in premature labour. Terbutaline was shown to be significantly more effective than placebo in inhibiting premature labour. At the Department of Obstetrics and Gynaecology, University Hospital, Lund, during the investigation period, 299 women gave birth to children with a birth weight less than 2,500 g. From this number, the mothers with a gestational age exceeding 36 weeks, but delivering children with a birth weight less than 2,500 g, should be subtracted according to the selection criteria used in this study. This means that only about 15 per cent of the patients with premature labour were accepted for the study, as patients with toxæmia, uterine malformations, fever, ruptured membranes, twins, vaginal bleedings, or a dilatation of the cervix exceeding 4 cm were excluded.

Zlatnik (1972), discussing this problem in connection with therapy with ethanol, found that 23 per cent of the patients with premature labour could be accepted for therapy. This agrees well with the present results.

In the present study, terbutaline was effective in 80 per cent of the selected cases. Differences of clinical value concerning effectiveness and side effects between terbutaline and drugs with

similar actions, for instance, ritodrine, fenoterol, and salbutamol, are difficult to demonstrate in humans and are not, so far, indicated in reported data.

Combinations of β -receptor stimulators and other drugs, such as verapamil (Weidinger and Wiest, 1973), and ethanol and pregnenolone sulphate (Bieniarz et al., 1971) have not produced convincingly better results. Recently, another approach to treatment of premature labour has been reported. Indomethacin, a blocker of prostaglandin synthesis, seems to effectively arrest premature labour (Zuckerman et al., 1974). From a theoretical point of view, a combination of a β -receptor stimulator and a blocker of the synthesis of prostaglandins might be an interesting alternative to evaluate as a treatment of premature labour.

5. GENERAL SUMMARY AND CONCLUSIONS

The present work has investigated, in vitro and in vivo, the effects of the selective β_2 -receptor stimulator terbutaline on human myometrial activity during pregnancy. The results are summarized as follows:

In vitro

The β -receptor stimulators isoprenaline and terbutaline inhibited the contractile activity of myometrial strips taken from the lower uterine segment at caesarean sections performed at term. This effect was blocked by propranolol, but was unaffected by phenoxybenzamin and also by practolol and H93/26. The results were obtained in normally polarized and also depolarized preparations. The actions of the different β -receptor blockers on the effects of isoprenaline and terbutaline, and the potency ratio between the two amines suggest that the adrenoceptor of the human uterus is of β_2 -type.

In vivo

The in vivo effects of terbutaline at term could be correlated with findings in vitro. Infusions of terbutaline 10 – 20 $\mu\text{g}/\text{min}$ or intravenous injections 250 μg effectively inhibited both spontaneous and oxytocin-induced uterine activity without adverse effects on the circulation of mother and child. Propranolol, 1 – 2 mg intravenously, blocked the inhibitory effect of terbutaline.

Terbutaline was also shown to depress uterine activity in vivo in the second trimester abortion induced by hypertonic saline or prostaglandin $\text{F}_{2\alpha}$.

A double-blind placebo-controlled study showed that terbutaline was a potent inhibitor of premature labour in patients fulfilling the selection criteria used in this investigation.

It is concluded that a safe and effective inhibition of human

uterine activity can be obtained by stimulating the β -receptors of the uterus with terbutaline. In many situations, there are indications for arresting the uterine activity during term labour; for instance, uterine hyperactivity, transportations, during the preparation for caesarean sections, and during X-ray investigations. Terbutaline, injected intravenously, in a dose of 250 μg , immediately relaxes the uterus for at least 20 minutes. Intravenous infusion therapy is recommended for arresting uterine activity for longer periods. Terbutaline is also recommended for treatment of premature labour in selected cases.

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RELAXING EFFECTS OF β -RECEPTOR STIMULATORS IN ISOLATED,
GRAVID HUMAN MYOMETRIUM

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SUMMARY

The effects of isoprenaline and the selective β_2 -receptor stimulator terbutaline were investigated on strips from human myometrium obtained at caesarean sections. In normally polarized preparations both amines (isoprenaline 0.02 - 0.4 $\mu\text{g/ml}$, terbutaline 0.2 - 8 $\mu\text{g/ml}$) decreased the frequency and the amplitude of the spontaneous contractile activity. This action was not affected by phenoxybenzamine, 0.5 $\mu\text{g/ml}$, but could be blocked by propranolol, 0.1 $\mu\text{g/ml}$. In myometrial strips, depolarized by increasing the extracellular potassium concentration, isoprenaline, 0.004 - 0.4 $\mu\text{g/ml}$, and terbutaline, 0.008 - 8 $\mu\text{g/ml}$, had relaxing effects that were unaffected by phenoxybenzamine, 0.5 $\mu\text{g/ml}$, but could be blocked by propranolol, 0.1 $\mu\text{g/ml}$. It is concluded that the effects of the tested amines are mediated by actions on β -adrenocentors, probably β_2 -receptors.

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INTRODUCTION

As first described by Ahlquist (1), relaxation-mediating β -receptors can be demonstrated in the isolated uterus of various animals (e.g., rat, rabbit, cat). This has been confirmed by several workers using different β -receptor stimulators (2,3,4,5). Inconsistent results have been reported on the effects of β -receptor stimulators on isolated human uterine muscle. Many authors have found these drugs ineffective for inhibition of tone and spontaneous contractile activity in strips from gravid and non-gravid human myometrium (6,7,8,9,10). This has been interpreted to mean that the human myometrium contains few or no β -receptors (8). However, other workers have demonstrated relaxing effects by isoprenaline on isolated human uterus. These effects could be blocked by β -receptor blocking agents, indicating the presence of β -receptors in this muscle (11,12,13).

The conflicting results obtained in previous studies stimulated us to re-investigate the effects of isoprenaline on gravid human uterine muscle, and also to test the actions of the selective β_2 -receptor stimulator terbutaline (14) on this tissue. In the present experiments, the effects of these amines were studied on isolated strips of human uteri obtained at caesarean section.

METHODS

From 13 patients, aged 24-38 years, small pieces from the lower uterine segment were obtained at caesarean sections performed at term. From the muscle pieces, 53 preparations were dissected, approximately 15-25 mm long, 2-4 mm wide, and 1 mm thick. Within 1 h after the operation, 47 of the preparations were mounted vertically in jacketed, temperature-controlled organ baths (25 ml) filled with Krebs solution of the following composition (mM): NaCl 118.0, KCl 4.6, CaCl_2 2.5, MgSO_4 1.15, NaHCO_3 24.9, KH_2PO_4 1.15, glucose 5.5, pH 7.4. This solution was maintained at 37°C and aerated with a mixture of 5 per cent CO_2 and 95 per cent O_2 . Parts of the muscle tissue from 3 of the patients were

stored in Krebs solution overnight (about 16 h) at 6°C. From these specimens 6 muscle strips were prepared. No qualitative differences were observed between the responses of these preparations and of those that were used immediately after the operation. 2-4 strips from each muscle piece were run simultaneously to facilitate the evaluation of the drug effects by providing adequate controls.

All the preparations used exhibited spontaneous contractile activity which, during the period of stabilization, developed a very regular pattern. 30 of the strips were depolarized by a solution in which the sodium of the normal Krebs medium was replaced by equivalent amounts of potassium. These strips were also given a period of stabilization of at least 1 h before the experimental procedures began.

Solutions were prepared on the day of the experiment. Double distilled water and analytical grade chemicals were used.

Drugs. The following drugs were used: (+)-isoprenaline hydrochloride (Sigma Chemical Company, USA), (+)-terbutaline sulphate (AB Draco, Sweden), (-)-nor-adrenaline bitartrate (Sigma Chemical Company, USA), (-)-adrenaline bitartrate (Sigma Chemical Company, USA), propranolol hydrochloride (ICI Ltd., England), phenoxybenzamine hydrochloride (Smith, Kline and French, England).

The drugs were injected directly into the bath, and mixing was almost instantaneous because of the aeration system. Concentrations given in the following refer to final bath concentrations.

RESULTS

a. Normally polarized muscle. The spontaneous activity of a uterine muscle strip showed a very regular pattern with contractions lasting for 0.5-1.5 min and appearing at intervals varying from 3 to 8 min in the different preparations. The amplitude of the contractions was in the range of 0.5-3 g.

Isoprenaline, 0.02-0.4 $\mu\text{g/ml}$, and terbutaline, 0.2-8 $\mu\text{g/ml}$, inhibited the spontaneous contractile activity of all the tested preparations.

The two amines decreased both the frequency and the amplitude of the contractions (Fig. 1); in many preparations, the drug concentrations used were sufficient to abolish the activity. Washing out the amines caused the strips to gradually recover their normal responses within approximately 10-20 min. In a few preparations, where the spontaneous activity had ceased after addition of one of the amines to the bath, a gradual but slow and incomplete recovery of the activity was observed while the drug was still present in the external medium.

The effect of propranolol on the actions of isoprenaline and terbutaline was evaluated in strips from 6 patients. After pretreatment of the preparations with propranolol (0.1 $\mu\text{g/ml}$), isoprenaline and terbutaline, in the concentrations indicated above, had no effects on either the frequency or the amplitude of the contractile activity. Propranolol also caused a preparation inactivated by one of the amines to resume its normal activity (Fig. 1).

In control experiments, propranolol generally did not influence the frequency or amplitude of the contractile activity of a muscle strip. In preparations from one of the patients, however, the addition of propranolol was associated with a slight increase in contraction frequency and amplitude.

Noradrenaline and adrenaline, 0.1-0.4 $\mu\text{g/ml}$, increased the spontaneous activity of the strips; this effect was completely blocked by phenoxybenzamine 0.1-0.5 $\mu\text{g/ml}$ (Fig. 1). Addition of noradrenaline or adrenaline to a preparation pre-treated with phenoxybenzamine caused an inhibition of the spontaneous activity. Phenoxybenzamine in these concentrations had no effect on the frequency and amplitude of the contractions and did not influence the inhibitory effects of isoprenaline and terbutaline (Fig. 1).

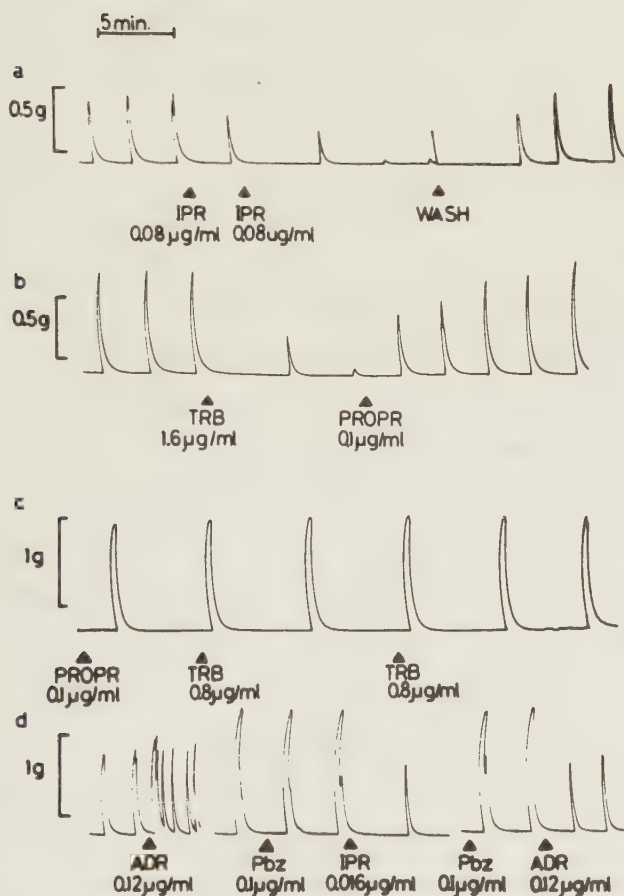


FIG. 1

Spontaneously active preparations. a: Isoprenaline (IPR) inhibits the contractile activity which gradually returns when the amine is washed out. b: Terbutaline (TRB) inhibits the contractile activity which gradually returns when propranolol (PROPR) is added to the bath. c: After pre-treatment with propranolol (PROPR), terbutaline (TRB) has no inhibiting effect. d: Adrenaline (ADR) increases the frequency and amplitude of the contractile activity. After pre-treatment with phenoxybenzamine (Pbz), isoprenaline (IPR) and adrenaline inhibit the contractile activity.

b. Depolarized muscle. Similar to rat uterus (15), human myometrium responded to an increase in extracellular potassium concentration with a transient contracture that did not relax completely, but levelled off to a new, stable baseline (Fig. 2). The maximal amplitude of the contracture was 1.5-4.0 g, and the tension level during maintained depolarization lay between 200 and 1600 mg.

Both isoprenaline and terbutaline in low concentrations (0.004-0.4 $\mu\text{g/ml}$ and 0.008-8 $\mu\text{g/ml}$, respectively) relaxed the depolarized muscle strip (Fig. 2). The degree of relaxation varied between different preparations, but the response depended on the tension level from which it began. Thus, at a high starting tension, the relaxing effect produced by a given concentration of one of the amines was more pronounced than at a low. The maximal decrease in tension ranged from 100 to 600 mg. In the individual muscle strip, the degree of relaxation was related to the concentration of drug in the bath. When a maximal response to one of the amines had been obtained, the addition of the other did not cause a further decrease in tension. Washing out the amines from the high-potassium medium caused the strip to increase its tension, but the starting level was not always attained (Fig. 2).

Pre-treatment of the preparations with propranolol (0.1 $\mu\text{g/ml}$) blocked the relaxing effect of the two investigated amines (Fig. 2). When propranolol was added to the external medium of a preparation relaxed by isoprenaline or terbutaline, the tension immediately began to increase. Propranolol by itself, in the concentration used, had no contracting effect on the depolarized uterine muscle (Fig. 2).

Depolarized myometrial strips were contracted by noradrenaline 0.1-1.2 $\mu\text{g/ml}$ (Fig. 2), and this contraction was completely inhibited by phenoxybenzamine (0.1-1 $\mu\text{g/ml}$). Phenoxybenzamine by itself did not increase the tension of the preparation and had no influence on the relaxing actions of isoprenaline and terbutaline.

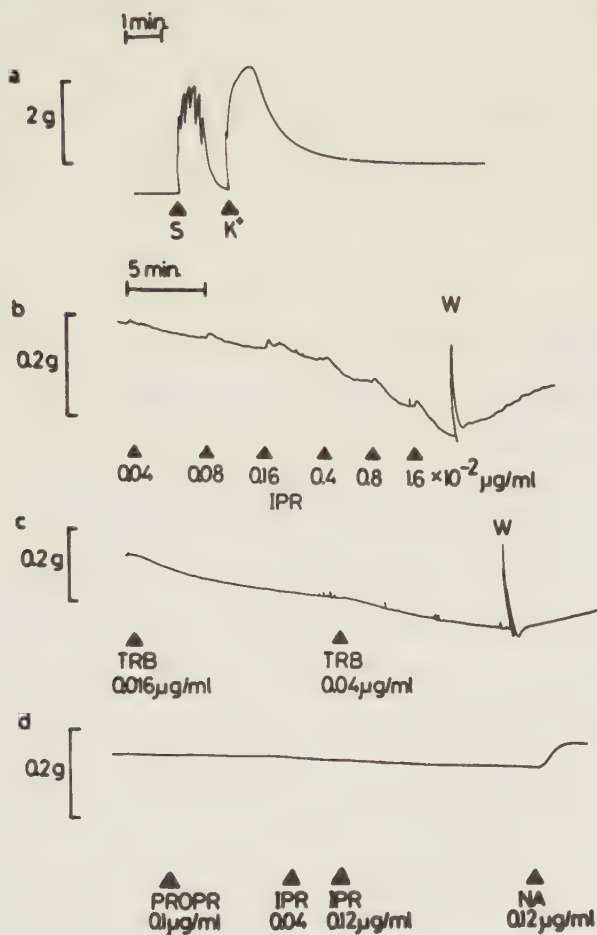


FIG. 2

Depolarized preparations. a: Spontaneous contraction (S) and a potassium contracture (K^+). b and c: Relaxing effects of isoprenaline (IPR) and terbutaline (TRB). Tension increases when the amines are washed out (W). d: In the presence of propranolol (PROPR), isoprenaline (IPR) has no relaxing effect, but noradrenaline (NA) contracts the preparation.

DISCUSSION

The present results showed that isoprenaline and terbutaline inhibited the spontaneous contractile activity of isolated, gravid human myometrium. This agrees with the findings of Stander and Barden (16) and Landesman and Wilson (12), who demonstrated inhibitory effects of isoprenaline on strips of human uterine muscles of different stages of gestation. On the other hand, according to Grün, Hillemans and Fleckenstein (10), β -receptor stimulators had very weak or no inhibiting effect on the spontaneous activity of isolated, gravid and non-gravid human myometrium; these drugs could even increase the frequency and amplitude of the contractions. Sullivan and Marshall (13) demonstrated that in the isolated, non-gravid human myometrium, isoprenaline in low concentrations (comparable to those used in the present study) relaxed carbamylcholine-induced contractures. This was interpreted as a β -receptor mediated effect as it could be blocked by propranolol. In high concentrations, isoprenaline was found to have contracting effects apparently mediated by stimulation of α -receptors, as they were inhibited by phentolamine (13).

The present study showed that the inhibiting effects of isoprenaline and terbutaline were unaffected by α -receptor blockade, but could be prevented by pre-treatment with propranolol. This agent could also make a preparation, inactivated by one of the amines, resume its contractile activity. These findings strongly suggest that the inhibition of the spontaneous activity produced by the two amines is mediated by β -adrenoceptors in the myometrium. This view was supported by the fact that the stimulating effects of noradrenaline and adrenaline were reversed into inhibition when the α -receptors had been blocked by phenoxybenzamine.

The presence of relaxation-mediating β -receptors in human uterine muscle is consistent with in vivo findings which show that both isoprenaline (17) and terbutaline (Ingemarsson, unpublished results) inhibit uterine motility at term. In animals, terbutaline proved to be a selective β_2 -receptor stimulator; iso-

prenaline was approximately 500 times more active than terbutaline on the β_1 -receptors of the heart, but only 20 times more active on the β_2 -receptors of the lung (14).

The potency ratio between the two amines, as indicated by the present experiments, suggests that the β -receptors of the human myometrium are β_2 -receptors. Also in animals, the uterine β -receptors have been classified as β_2 -receptors (3).

Edman and Schild (15) and Schild (4), demonstrated that the depolarized rat uterus is very sensitive to the relaxing effects of isoprenaline. Schild (4) also showed that the relaxation was mediated by β -receptors. In depolarized, non-gravid human myometrium, Sullivan and Marshall (13) demonstrated excitatory responses to noradrenaline and adrenaline, but were unable to find any relaxing effect of isoprenaline. They suggested therefore that this action of isoprenaline was dependent on a normally polarized membrane. The present study revealed that excitatory responses could be obtained by noradrenaline in the denolarized, gravid human uterus, but also that both isoprenaline and terbutaline in low concentrations had relaxing effects. The relaxation produced by the amines could be blocked by propranolol but was not affected by phenoxvbenzamine. These findings suggest that isoprenaline-induced relaxation of denolarized human uterine muscle is mediated by stimulation of β -receptors, and that a normal membrane potential is not a prerequisite for this effect.

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EFFECTS OF TERBUTALINE ON HUMAN UTERINE MOTILITY AT TERM

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Abstract. The effects of the selective β_2 -receptor stimulator terbutaline on the activity of gravid, human myometrium were investigated in vitro and in vivo, before and after administration of different β -receptor blockers. Terbutaline, 0.2–1.0 $\mu\text{g/ml}$, inhibited the spontaneous contractile activity of isolated strips of myometrium. This effect was unaffected by the selective β_1 -receptor blockers practolol, 1 $\mu\text{g/ml}$, and H 93/26, 1 $\mu\text{g/ml}$. However, the non-selective blocker propranolol, 0.1 $\mu\text{g/ml}$, completely inhibited the terbutaline effects. The in vitro effects of terbutaline could be correlated with findings in vivo. Intra-uterine pressure was recorded in 4 pregnant women at term. Infusion of terbutaline, 10–15 $\mu\text{g/min}$, for 20–40 min, effectively inhibited both spontaneous and oxytocin-stimulated uterine activity. There was a moderate increase in maternal heart rate, but no consistent effect on maternal blood pressure. Fetal heart rate was little affected. The uterine effects of terbutaline were not influenced by practolol, 5–20 mg i.v., but completely inhibited by propranolol, 1–2 mg i.v. The results suggest that terbutaline inhibits uterine motility by effects on uterine β_2 -receptors and that it can be given in clinically effective doses without adverse circulatory effects on mother or fetus.

Sympathomimetic drugs are known to influence the activity of the human uterus at term (8, 19). Adrenergic substances with stimulating effects mainly on α -receptors, e.g., noradrenalin, increase uterine tone and frequency and amplitude of uterine contractions (19), whereas those exerting their effects through stimulation of β -receptors, e.g., isoprenaline, have the opposite effects (17). β -receptor stimulation involves effects not only on uterus, but also actions on, e.g., heart, bronchi, and peripheral vessels, clinically resulting in tachycardia, bronchodilation, and hypotension. However, in animals, Lands et al. (15) showed that the β -receptors mediating the cardiac effects (β_1) can be separated from those associated with uterine and bronchial

relaxation and with peripheral vasodilatation (β_2). These findings have largely been confirmed in humans.

The development of adrenergic β -receptor stimulators with effects mainly on β_2 -receptors has led to an extensive use of these drugs as bronchodilators, and has evoked new interest also in their clinical use as uterine relaxants. Terbutaline, which may be classified as a selective β_2 -receptor stimulator (18), was previously shown to effectively inhibit the spontaneous contractile activity of isolated, gravid human myometrium (1). The present investigation was undertaken in order to further investigate the in vitro effects of terbutaline on human uterus before and after blockade with different β -receptor blocking agents and to correlate these findings with effects in vivo. Therefore the effects of terbutaline on spontaneously active and oxytocin-stimulated human uterus at term was studied in patients by means of intrauterine pressure recordings (5). Also in vivo the interaction between terbutaline and the β -receptor blockers propranolol and practolol was investigated.

MATERIALS AND METHODS

In vitro. Nineteen strips from the lower uterine segment were obtained from 7 patients, aged 22–29 years, undergoing caesarean section at term. The strips were dissected and mounted in organ baths as previously described in detail (1). Mechanical activity was recorded by means of force transducers (Grass Ft 03).

In vivo. The uterine activity of 4 pregnant women at term was continuously monitored for 3–5 h. A spongetipped catheter (5) with an outer diameter of 1.8 mm was inserted through the cervical canal and placed in the uterine cavity between the membranes and the uterine wall. Changes in intra-uterine pressure were recorded by means of a pressure transducer (Hewlett Packard, model

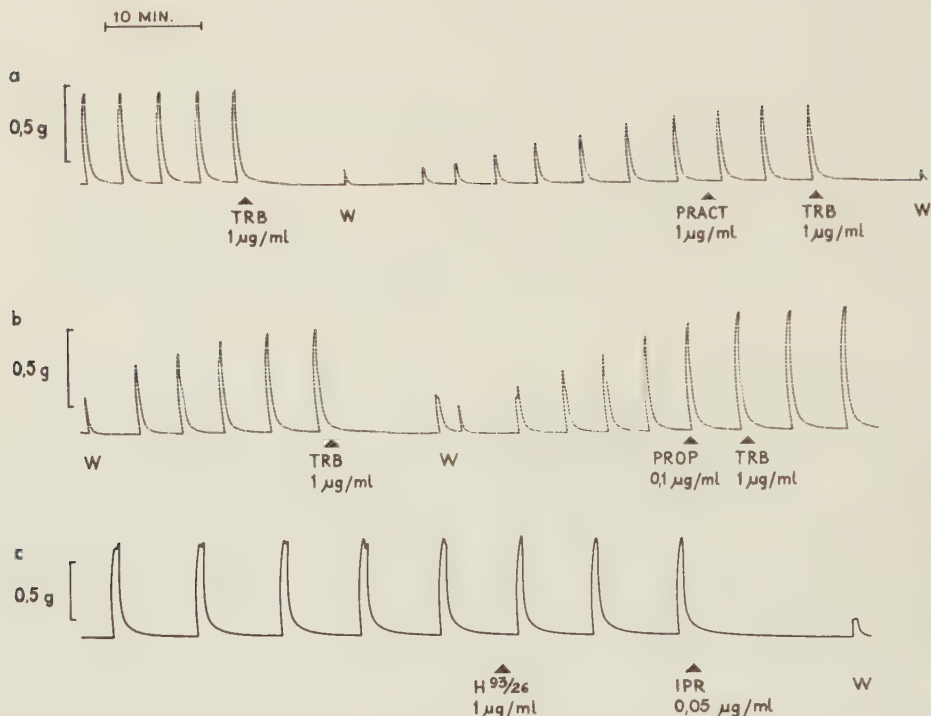


Fig. 1. Effects of terbutaline (TRB) and isoprenaline (IPR) on isolated uterine strips. (a) Terbutaline, 1 µg/ml, inhibits the spontaneous contractile activity. This effect is not prevented by practolol (PRACT), 1 µg/ml.

(b) Propranolol (PROP), 0.1 µg/ml, completely inhibits the effects of terbutaline, 1 µg/ml. (c) H 93/26, 1 µg/ml, has no effect on the inhibitory action of isoprenaline, 0.05 µg/ml. W=washing.

1280B) on a cardiocograph (Hewlett Packard, model 8020A). The intensity of uterine contractions was measured as the rise in intra-uterine pressure in mmHg. Frequency was expressed as the number of contractions per 10 min. Uterine activity was expressed in Montevideo Units and calculated for each 10 min period. Fetal heart rate was recorded on the cardiocograph using an ultrasonic flow detector (Hewlett Packard). Maternal blood pressure and heart rate were monitored throughout the investigation by percutaneous insertion of a polyethylene catheter (Stille-Werner, Sweden) into the radial artery. The catheter was connected to a pressure transducer (EMT 746, Elema Schönander, Sweden) and the blood pressure was recorded by means of an ink-jet recorder (Mingograph 81, Elema Schönander, Sweden).

Oxytocin and terbutaline were infused intravenously by means of an infusion pump (IVAC 501, AGA, Sweden) through catheters placed in forearm veins. Propranolol and practolol were injected intravenously for 2–5 min. Before the administration of terbutaline, propranolol, and practolol, uterine activity was recorded for a control period of at least 1 h.

Drugs. The following drugs were used: oxytocin (Syn-tocinon, Sandoz, Switzerland), $\pm$ terbutaline sulphate (Draco, Sweden), *d,l*-propranolol chloride (ICI, England), practolol (ICI, England), H 93/26 tartrate, 1-4-(2-methoxyethyl)-phenoxy-3-isopropylaminopropan-2-ol (Hässle, Sweden).

RESULTS

In vitro

After mounting in the muscle baths, all strips used for the experiments developed spontaneous contractile activity during an initial period of stabilization (1–2 h). In accordance with previous findings (1), terbutaline (0.2–1.0 µg/ml) and isoprenaline (0.02–0.05 µg/ml) were found to diminish the frequency and amplitude of the spontaneous contractions; in the concentrations used, the drugs usually abolished the contractile activity. The drug effects

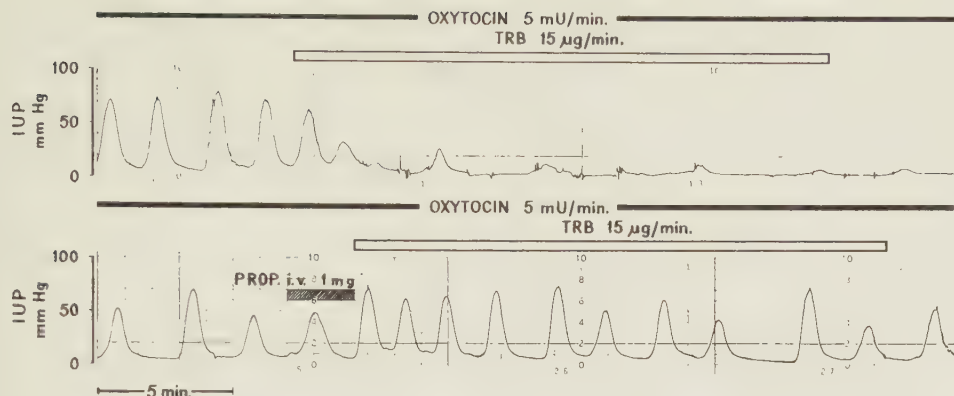


Fig. 2. Patient 1. Original record of intrauterine pressure (IUP). Infusion of terbutaline (TRB), 15 $\mu\text{g}/\text{min}$, effectively inhibits oxytocin-stimulated (5 mU/min) uter-

ine contractions (upper panel). Terbutaline infusion has no effect after pre-treatment with propranolol (PROP), 1 mg i.v. (lower panel).

were reversible, and after repeated washing, the preparation gradually increased its activity until control level was attained (Fig. 1).

The effects of the selective β_1 -receptor blocker practolol were investigated in 12 preparations. The drug was added to the bathing fluid to a final concentration of 1–10 $\mu\text{g}/\text{ml}$ and was left in contact with the preparations for 10–20 min. Practolol in these concentrations had by itself no effect on the spontaneous contractile activity of the strips. In a concentration of 1 $\mu\text{g}/\text{ml}$, practolol had no effect on the actions of terbutaline and isoprenaline (Fig. 1a). However, in concentrations of 5 and 10 $\mu\text{g}/\text{ml}$, practolol reduced but never abolished the inhibiting effects of the β -receptor stimulators.

H 93/26, a new selective β_1 -receptor blocker (21) had no effects on the spontaneous contractions of 9 myometrial strips when tested in the concentration range 1–10 $\mu\text{g}/\text{ml}$. H 93/26 in a concentration of 1 $\mu\text{g}/\text{ml}$ did not affect the actions of terbutaline and isoprenaline (Fig. 1c) on the strips, but similar to practolol, in the concentrations 5 and 10 $\mu\text{g}/\text{ml}$, it reduced but never abolished the effects of these drugs.

Propranolol, blocking both β_1 - and β_2 -receptors, did not affect the spontaneous activity of the preparations. The effects of both terbutaline and isoprenaline were completely inhibited by propranolol 0.1 $\mu\text{g}/\text{ml}$ (Fig. 1b) when this drug was added to the bath either before or after the administration of the β -receptor stimulators. The results with propranolol agree with previous findings (1).

In vivo

Patient 1 (31-year-old gravida I weighing 46 kg)

The patient arrived at the delivery department at term with spontaneous labour and intact membranes. The cervix was effaced and dilated 4 cm. Stimulation of the uterine activity with oxytocin infusion, 5 mU/min, was started and maintained throughout the investigation. Fig. 2 gives the original record of intra-uterine pressure changes. The patient had strong uterine contractions reaching a peak of 60–70 mmHg every 2 min. Infusion of terbutaline, 15 $\mu\text{g}/\text{min}$, had a prompt effect on the contractions. Their amplitude was depressed to less than 10 mmHg and the frequency was reduced to one contraction in 4–5 min. Fig. 3 summarizes the different measurements of uterine contractile activity and the effects on blood pressure and heart rate of mother and fetus. Uterine activity, expressed in Montevideo Units, diminished from 345 to a minimum of 15. There was a rise in maternal heart rate from 60 to about 100 beats/min, but without obvious effects on maternal blood pressure. The patient tolerated the infusion well and reported no side effects. Fetal heart rate rose from 150 beats/min before the terbutaline infusion to about 160 beats/min and were then steady at this level.

The terbutaline infusion was maintained for 20 min. After cessation of the infusion, the contractility of the uterus gradually returned and after 1 h and 50 min, the activity, expressed in Montevideo Units, reached about 65 % of the pre-infusion value.

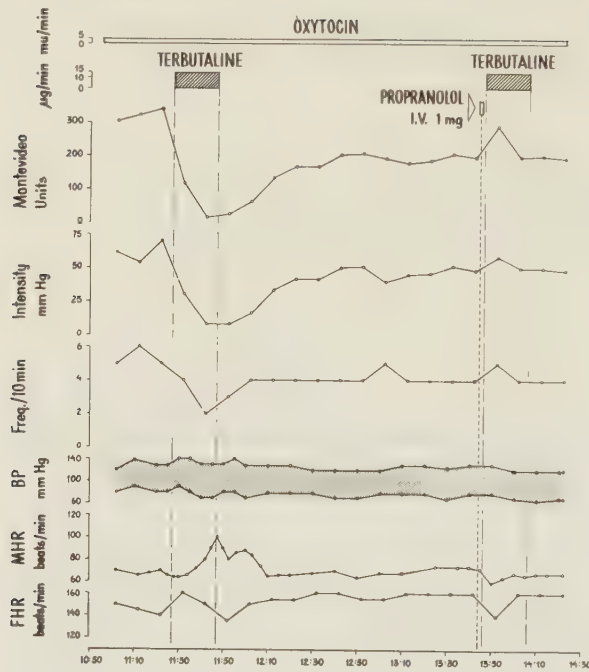


Fig. 3. Patient 1. Summary of the effects of terbutaline and propranolol on uterine activity (Montevideo Units), on intensity and frequency of uterine contractions, and on maternal blood pressure (BP), maternal heart rate (MHR), and fetal heart rate (FHR).

At this time propranolol, 1 mg, was injected intravenously for 2.5 min (Fig. 2 *b*). Immediately after the injection, a new terbutaline infusion was started at the same rate (15 $\mu\text{g}/\text{min}$) and for the same time (20 min) as before. After the administration of propranolol, an increase in the uterine activity dur-

ing the first 10 min of the terbutaline infusion was observed. Both the intensity and the frequency reached higher values, corresponding to an increase in activity from 200 to 290 Montevideo Units. During the last 10 min of the infusion, uterine activity resumed its pre-propranolol value. No inhibition

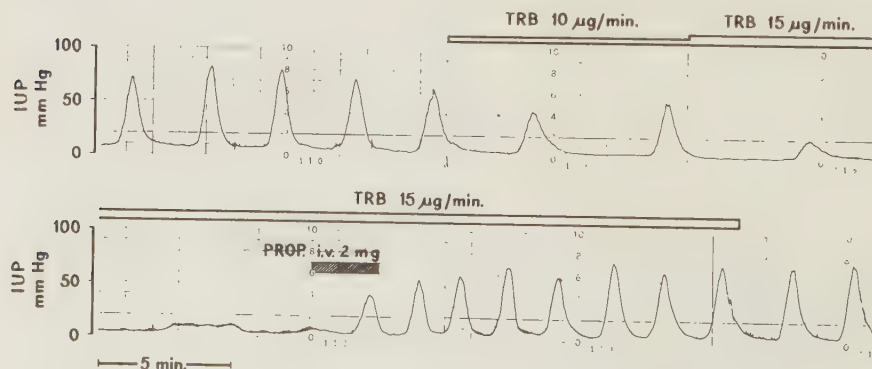


Fig. 4. Patient 2. Original record of intrauterine pressure (IUP). Infusion of terbutaline (TRB), 10–15 $\mu\text{g}/\text{min}$, inhibits uterine contractions (upper panel). After injection

of propranolol (PROP), 2 mg i.v., the contractile activity is resumed despite continuous infusion of terbutaline.

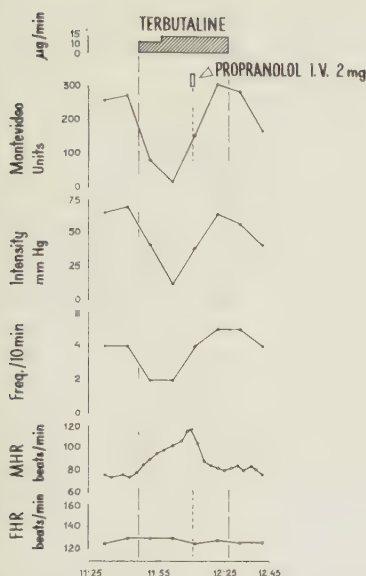


Fig. 5. Summary of the effects of terbutaline and propranolol on uterine activity, maternal blood pressure and heart rate, and on fetal heart rate.

of the uterine activity was observed. Maternal blood pressure and heart rate showed no significant alterations except for a small decrease in heart rate immediately after the injection of propranolol. Fetal heart rate decreased from 160 to 140 beats/min immediately after the propranolol injection, but returned to 160 beats/min after a few minutes.

Delivery of a normal 3.0 kg infant occurred 5.5 hours after the end of the last infusion.

Patient 2 (22-year-old gravida II weighing 63 kg)

The patient was in spontaneous labour and the cervix was effaced and dilated 5 cm when recording of uterine activity was started. The membranes were intact. Fig. 4 shows the original record of intrauterine pressure changes, and Fig. 5 summarizes the observations made. Contractions occurred every 2.5 to 3 min with an average intensity of 65 mmHg. Infusion of terbutaline, $10 \mu\text{g/min}$, produced a decrease in the intensity of the contractions to an average of 45 mmHg and a reduction in frequency to one contraction every 4.5 to 5 min. After 9 min, the infusion rate was increased to $15 \mu\text{g/min}$ and this reduced the intensity of the contractions to less than 10 mmHg. The

frequency did not change markedly. Maternal heart rate increased during the infusion from 78 beats/min to a maximum of 116 beats/min. The patient tolerated the infusion well and reported no side effects except for slight palpitations. After 24 min, 2 mg of propranolol was injected during 2.5 min, the terbutaline infusion rate being maintained at $15 \mu\text{g/min}$. This resulted in an increase in uterine contraction frequency; uterine activity, expressed in Montevideo Units, temporarily increased to a higher level than before the terbutaline infusion. Maternal heart rate was reduced after propranolol administration and reached the pre-infusion value about 10 min after the injection. Maternal blood pressure was measured by auscultation every 3 min during the investigation and showed no alterations. Fetal heart rate was not affected by the infusion of terbutaline or the injection of propranolol.

Delivery of a normal 2.4 kg infant occurred 4.5 h after the end of the terbutaline infusion.

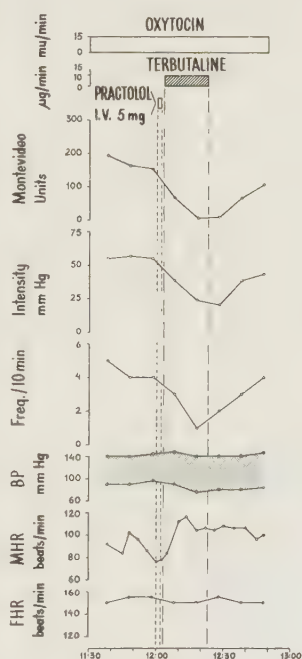


Fig. 6. Patient 3. Summary of the effects of terbutaline infusion ($10 \mu\text{g/min}$) on uterine activity, maternal blood pressure and heart rate. Uterine activity is stimulated with oxytocin, 15 mU/min. Practolol, 5 mg i.v., has no effect on the action of terbutaline.

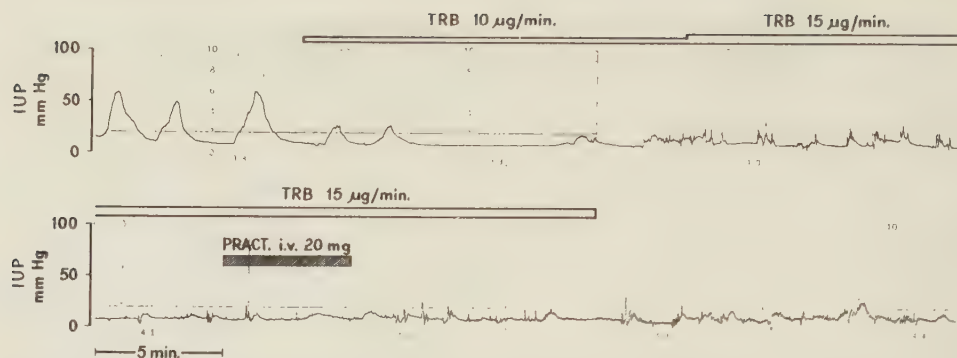


Fig. 7. Patient 4. Original record of intrauterine pressure (IUP). Infusion of terbutaline (TRB), 10–15 $\mu\text{g}/\text{min}$, effectively inhibits uterine activity (upper panel). Prac-

tocol, 20 mg i.v., has no effect on this action. Cf. the effects of propranolol (Fig. 4).

Patient 3 (28-year-old gravida II para I weighing 89 kg)

The patient was in labour maintained throughout the investigation with infusion of oxytocin, 15 mU/min. Fig. 6 summarizes the different observations made. The uterine contractions occurred approximately every 2.5 min, and had an average intensity of 55 mmHg. The cervix was at this moment dilated 4 cm. Practolol, 5 mg, was injected intravenously during 2 min, immediately followed by infusion of terbutaline, 10 $\mu\text{g}/\text{min}$, for 20 min. The infusion produced a marked decrease in the uterine activity, from 160 to less than 10 Montevideo Units (Fig. 6). There was a moderate increase in maternal heart rate to a peak value of 116 beats/min, but no obvious effects on the blood pressure. Fetal heart rate was steady at about 150 beats/min.

The patient reported no side effects during the infusion.

After cessation of the terbutaline infusion, the uterine work gradually increased but had not reached its pre-existing activity after 30 min, mostly because the contractions had a lower intensity than before the infusion. Maternal heart rate did not decrease when the infusion was stopped but was unchanged for at least 30 min.

After rupture of the membranes there was a normal delivery of a 3.8 kg infant 2 h after the end of the infusion.

Patient 4 (21-year-old gravida I weighing 76 kg)

The patient was in spontaneous labour with intact membranes and the cervix dilated 4 cm when re-

cording of uterine activity started. Fig. 7 shows the original recording of intrauterine pressure changes, and Fig. 8 summarizes the different observations made. Contractions occurred every 3 min with an average intensity of 45 mmHg. Infusion of terbutaline, 10 $\mu\text{g}/\text{min}$, was started and

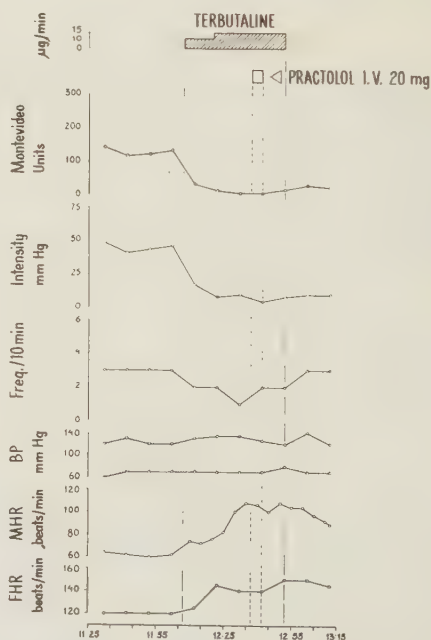


Fig. 8. Patient 4. Summary of the effects of terbutaline and practolol on uterine activity, maternal blood pressure and heart rate, and on fetal heart rate.

the infusion rate was increased to 15 $\mu\text{g}/\text{min}$ after 15 min. The infusion produced a decrease in uterine activity from 134 to 10 Montevideo Units, mainly due to a decrease in the intensity of the contractions. There was an increase in the maternal heart rate from about 65 beats/min to a peak value of 108 beats/min. Fetal heart rate increased from 120 to a maximum of 150 beats/min. After about 30 min practolol, 20 mg, was injected at a rate of 4 mg/min during maintained terbutaline infusion. There were no obvious changes in the uterine activity, maternal heart rate, blood pressure and fetal heart rate. The patient reported no side effects during the infusion.

When the terbutaline infusion was stopped after 45 min, the frequency of the contractions returned to the pre-existing level, but they showed the same low intensity as during the infusion for a further 25 min. Maternal blood pressure and fetal heart rate were unchanged, but the maternal heart rate gradually decreased to 84 beats/min during the period of recording.

Normal delivery of a 3.4 kg infant occurred 4.5 h after the end of the infusion.

DISCUSSION

Adrenergic β -receptor stimulators have been used clinically for several years in order to produce inhibition of premature and term labour (see, e.g. 13, 16). Agents such as isoprenaline and orciprenaline, which have marked effects on the cardiac β -receptors (β_1) in doses necessary for effective inhibition of uterine motility, also produce maternal tachycardia and hypotension and increase the risk of cardiac arrhythmias (17, 20). This limits the clinical value of these drugs.

Several β -receptor stimulators, reported to produce uterine relaxation with only minor cardiac effects, have been investigated clinically, e.g., ritodrine (4, 12, 14), fenoterol (Th 1165a) (9) and salbutamol (16). Terbutaline has been shown to stimulate mainly β_2 -receptors (18) and is one of the most selective β_2 -receptor stimulators presently available (7, 11). The drug is widely used clinically in the treatment of bronchial asthma and is able to produce bronchodilation without significant cardiac effects (see, e.g., 2, 3). In a previous investigation on isolated strips of gravid human uterus (1), it was demonstrated that the β -receptors of human myometrium could most probably be classified as

β_2 -receptors, and that terbutaline effectively reduced the frequency and amplitude of the spontaneous contractile activity of this tissue. The present results confirm these findings.

When tested *in vitro*, the selective β_1 -receptor blockers practolol (10) and H 93/26 (21) did not influence the inhibiting effects of terbutaline and isoprenaline except when used in high concentrations. On the other hand, propranolol, blocking both β_1 and β_2 -receptors, completely inhibited the effects of the two amines. Also *in vivo*, it could be demonstrated that terbutaline effectively inhibited spontaneous as well as oxytocin-induced labour. Both the frequency and the intensity of the uterine contractions were diminished, and uterine activity, expressed in Montevideo Units, was reduced to less than 10 per cent of the control value. Similar to the findings in isolated myometrial strips, propranolol made the uterus, relaxed by terbutaline, resume and even increase its activity above the control level, and pretreatment with propranolol completely inhibited the relaxing action of terbutaline. In contrast, practolol did not affect the actions of terbutaline on uterine motility. Thus, there was a good correlation between the effects of terbutaline and the β -receptor blockers on isolated uterine tissue and on the uterus *in situ*.

During infusion of terbutaline there was a tolerable increase in maternal heart rate, but no significant effects on maternal blood pressure. The positive chronotropic effect, which can be expected to be a main side effect when high doses of terbutaline are given, can probably be ascribed not only to a direct stimulation of the cardiac β -receptors, but also to a reflex adjustment to peripheral vasodilatation (2). Though practolol had no definite effect on the increase in heart rate produced by terbutaline in the 2 patients tested, it may be possible to control excessive tachycardia with β_1 -receptor blockers such as practolol and H 93/26 without interfering with the uterus-relaxing effect of terbutaline. In support of this view, tachycardia produced by ritodrine was successfully controlled by practolol (6).

In 3 of our 4 cases no consistent effect on fetal heart rate was observed during infusion of terbutaline; but in one, there was a moderate increase from 120 to 150 beats/min.

Although preliminary, the present results suggest that effective inhibition of uterine activity at term can be obtained with terbutaline without ad-

verse effects on maternal or fetal circulation. Further clinical evaluation of the effects of terbutaline in premature and term labour is in progress.

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The relaxing effect of terbutaline on the human uterus during term labor

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The uterine and cardiovascular responses to the adrenergic β_2 -receptor stimulator terbutaline (TRB) were investigated in 14 patients in normal term labor. TRB, administered intravenously at a rate of 10 to 20 μ g per minute, effectively inhibited uterine activity in advanced labor and also expulsion. Intravenous injection of TRB, 250 μ g, diminished oxytocin-induced uterine hyperactivity. No serious side effects of the drug were observed; the circulatory effects were minimal, except for a tolerable maternal tachycardia. The mode of action and clinical application of TRB for inhibition of unwanted uterine activity are discussed.

IN OBSTETRIC practice, depression of uterine activity is often desirable; for instance, in threatened abortion, threatened premature labor, and myometrial hyperactivity in term labor. In the long history of obstetrics, many drugs have been tried in order to achieve such depression, but usually their effectiveness has been moderate and/or their usefulness limited by severe side effects. Adrenergic β -receptor stimulators are an important group of agents used for uterine inhibition. Animal as well as human uterus contains β -receptors which may be classified as β_2 -receptors.^{1, 15} Consequently, in order to depress uterine activity, agents with stimulating effects mainly on β_2 -receptors are preferable, because excessive cardiovascular effects of nonselective β -receptor stimulators can be avoided.

In recent years, several agents with rather selective β_2 -receptor-stimulating effects have become available for depressing uterine activity—e.g., rito-

drine,^{5, 6, 14} fenoterol (Th 1165a),¹⁸ salbutamol¹⁶—and the results have been promising.

In animal experiments, terbutaline (TRB) has proved to have selective effects on β_2 -receptors.^{10, 21} The drug was demonstrated to inhibit the spontaneous contractile activity of isolated human myometrium at term¹ and also to effectively decrease uterine motility in patients in term labor.² The present investigation further examined the myometrial and cardiovascular effects of TRB during term pregnancy.

Patients and methods

All studies of the effect of drugs depressing uterine activity are hazardous because in threatened abortion, threatened premature labor, and the beginning of term labor, uterine activity frequently ceases spontaneously. In order to avoid this hazard, we studied the effect of TRB in stages of labor in which spontaneous decrease of uterine activity is rare, e.g., after the cervix is well effaced and dilated 4 cm. or more. Fourteen patients were studied. All were fully informed and gave their consent to the study. They were divided into two groups according to the obstetric situation.

Group I. In this group cervical dilatation was 4 to 5 cm. and the fetal head, in cephalic presentation, was engaged in the maternal pelvis. The membranes

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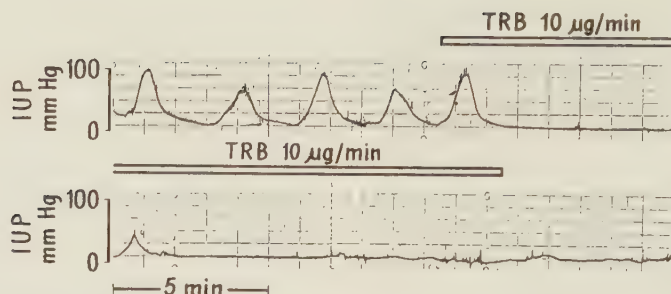


Fig. 1. The effect of TRB on uterine activity.

were intact. This group consisted of eight women, aged 20 to 31 years—six primiparas and two multiparas.

Group II. In this group cervical dilatation was 8 cm. or more and the fetal head, in cephalic presentation, was deeply engaged in the maternal pelvis. The membranes were intact. This group consisted of six women, aged 19 to 29 years—four primiparas and two multiparas. Two of them (No. 5 multipara, and No. 10, primipara) were in the second stage of labor.

For recording of uterine activity, a sponge-tipped catheter,⁷ outer diameter 1.8 mm., was inserted through the cervical canal between the membranes and the uterine wall. It was attached to a pressure transducer (Hewlett Packard, Model 1280B). Intra-uterine pressure (IUP) was recorded on a cardiotoctograph (Hewlett Packard, Model 8020A). The intensity of uterine contractions was measured as the increase in IUP in millimeters of mercury. Frequency was expressed as the number of contractions during 10 minutes. Uterine activity was expressed in Montevideo units and calculated for each 10 minute period.

Fetal heart rate was monitored on the cardiotocograph by means of an ultrasonic flow detector (Hewlett Packard).

Maternal blood pressure and heart rate were continuously recorded in nine of the patients after percutaneous insertion of a polyethylene catheter (Stille-Werner, Sweden) into the radial artery. The catheter was connected to a pressure transducer (EMT 746, Elema Schönander, Sweden) and blood pressure and ECG were recorded by means of an ink-jet recorder (Mingograph 81, Elema Schönander, Sweden). In the other five patients blood pressure was followed by indirect brachial pressure determinations every 5 minutes. The pulse frequency

Table I. Data on the administration of TRB

Pt. No.	TRB infusion rate (µg/min.)	Total infusion time (min.)	Body weight (Kg.)	Total amount of TRB given (µg)
1	10	20	78	200
2	5-10	20	77	170
3	10	20	68	200
4	10	22	82	220
5	10-15	25	62	350
6	10-20	40	82	650
7	10-15	25	65	285
8	10-15	25	72	300
9	10	40	69	400
10	10	20	73	200
11	15	20	76	300
12	10-15	40	64	555
13	10	20	89	200
14	10-15	45	76	600

was recorded simultaneously. Six of the patients received oxytocin, 5 to 15 mU. per minute, throughout the investigation to enforce the uterine activity.

Oxytocin and TRB were intravenously infused by means of an infusion pump (IVAC 501, AGA, Sweden) through catheters placed in forearm veins. TRB was given at a rate of 10 to 20 µg per minute for 20 to 45 minutes (Table I), the total average dose being 330 µg (range, 170 to 650 µg).

In all patients uterine activity was recorded during a control period of at least 30 minutes to obtain a baseline of activity before TRB was administered. After the TRB infusion, uterine activity was monitored for at least one hour and in most cases until delivery. The nonselective β -receptor blocker propranolol, 1 mg. intravenously, was given to two of the patients after the TRB infusion was stopped; to one patient, propranolol (2 mg. intravenously)

Table II. Uterine activity before and during infusion of TRB

	Uterine activity (M.U.)		Intensity (mm. Hg)		Frequency (contractions/10 min.)	
	Mean	Range	Mean	Range	Mean	Range
<i>Group I:</i>						
Before TRB	236	134-340	61	40-78	3.9	3-5
During TRB	15	0-36	9	0-18	1.3	0-2
<i>Group II:</i>						
Before TRB	244	180-328	52	35-64	4.7	4-5
During TRB	28	9-68	11	7-18	2.8	1-3

Table III. Effects of TRB on blood pressure

Pt. No.	Mean arterial BP (mm. Hg)			Systolic BP (mm. Hg)			Diastolic BP (mm. Hg)			Pulse pressure (mm. Hg)		
	Before in- fusion	Change during infusion		Before in- fusion	Change during infusion		Before in- fusion	Change during infusion		Before in- fusion	Change during infusion	
		Max. decrease	Max. increase		Max. decrease	Max. increase		Max. decrease	Max. increase		Max. decrease	Max. increase
2	108	1	2	155	0	5	85	5	0	70	0	10
3	78	6	0	105	0	0	65	10	0	40	0	10
5	82	0	8	115	0	15	65	0	5	50	5	10
7	100	0	2	130	0	5	85	0	0	45	0	5
8	102	12	0	135	5	0	85	15	0	50	0	10
10	95	0	5	125	0	5	80	0	5	45	5	0
11	93	1	4	130	0	5	75	5	5	55	5	10
13	103	4	4	140	0	10	85	10	0	55	0	15
14	85	2	8	115	0	25	70	5	0	45	0	25

was administered during the infusion of TRB; and to one, the selective β_1 -receptor blocker practolol (20 mg. intravenously) was given. During the investigation no other drugs were given to any of the patients.

Furthermore, to illustrate the therapeutic effectiveness of TRB, the drug was given to two patients who were developing clinical signs of uterine hyperactivity and changes in fetal heart rate, respectively, during oxytocin infusion. In one of them, IUP was monitored as described above; in the other, the uterine contractions were recorded by means of external tocography. TRB, 250 μ g, was administered to them as a single intravenous injection during 1 to 2 minutes.

Results

Effects on uterine contractions. In all patients TRB, infused at a rate of 10 to 20 μ g per minute, inhibited the uterine contractions. This is illustrated by the representative recording in Fig. 1. The effects are summarized in Figs. 2 and 3. Figs. 2 and 3 and Table II show that (1) the effect of TRB was independent of the stage of labor, as

effective inhibition of uterine activity was obtained in both Groups I and II; (2) the effect was practically immediate; (3) there was primarily a decrease in amplitude; (4) the frequency of contractions was also reduced.

Among the patients there was no difference in responses between those who received oxytocin and those who did not. During TRB infusion no tendency to decreased effectiveness of the drug ("uterine escape") was observed in any of the patients.

After the infusion had been stopped the uterine activity gradually returned to control level. In no case were signs of rebound activity observed. In three patients (Nos. 8, 10, and 12) receiving propranolol (1 to 2 mg. intravenously) after or during the TRB infusion, uterine activity immediately increased; in one case (No. 12) it even exceeded the control value (Figs. 2 and 3). In one patient (No. 14) given practolol (20 mg. intravenously) no effect on uterine activity was observed (Fig. 2).

Effects on maternal blood pressure and heart rate. The recorded changes in maternal arterial blood pressure were small. Most of the patients

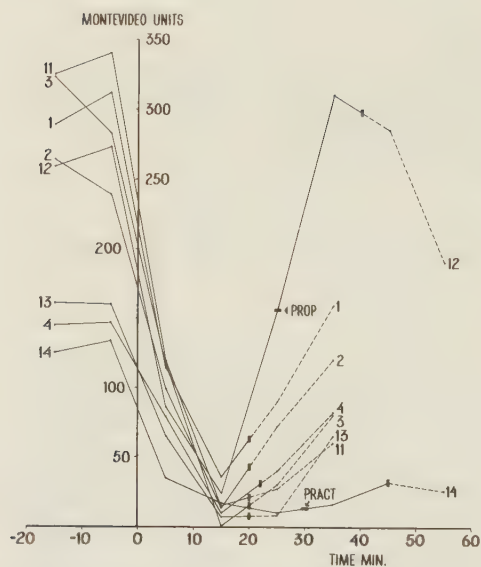


Fig. 2. The effects of TRB on uterine activity in Group I patients. Intravenous infusion of TRB was started at 0 time. Vertical bars, end of TRB infusion; horizontal bars, administration of propranolol (*PROP*), 2 mg. intravenously (patient No. 12), and practolol (*PRACT*), 20 mg. intravenously (patient No. 14). Hatched lines: uterine activity after stopping the TRB infusion.

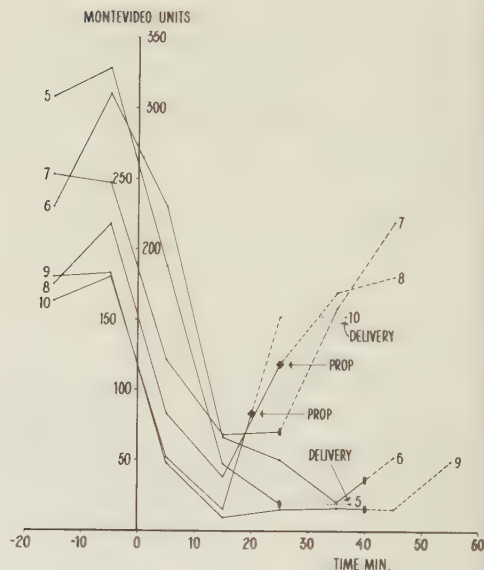


Fig. 3. The effects of TRB on uterine activity in Group II patients. Symbols as in Fig. 2. Propranolol (*PROP*), 1 mg. intravenously, was given to patients Nos. 8 and 10. Patients Nos. 5 and 10 were delivered 13 and 17 minutes, respectively, after the end of the TRB infusion. No recordings were obtained during the time indicated by dotted lines.

showed a slight increase in systolic pressure, a slight decrease in diastolic pressure, and, consequently, an increase in pulse pressure (Table III). The mean arterial blood pressure did not change significantly (Fig. 4). In one patient (No. 8) given propranolol (1 mg. intravenously) immediately after the TRB infusion had been stopped, a marked increase in blood pressure was recorded after injection of the β -receptor blocker, together with a reduction in heart rate.

The most prominent cardiovascular effect of TRB was an increase in heart rate (Fig. 5). The nine patients whose intra-arterial blood pressure was monitored showed a mean maximal increase from 80 to 119 beats per minute. No arrhythmias or pathologic ECG changes were observed. The increase in heart rate continued for a variable period after the end of the TRB administration. Only in one patient (No. 11), whose preinfusion heart rate was low (54 beats per minute), did the frequency drop immediately after the infusion was stopped, suggesting a high vagal tonus.

The three patients receiving propranolol showed an immediate decrease in heart rate to about control values. There seemed to be no effect on the increase in heart rate produced by TRB in the patient given practolol during infusion of the β_2 -receptor stimulator (Fig. 5, patient No. 14).

The five patients whose blood pressure was recorded by auscultation showed no significant changes of systolic and diastolic pressures. The mean preinfusion heart rate of these patients was 78 beats per minute (range, 54 to 95 beats per minute); during the infusion there was an increase to 112 beats per minute (range, 78 to 135 beats per minute). In patient No. 12 the heart rate increased from 72 to 118 beats per minute. After administration of propranolol (2 mg. intravenously) during continued TRB infusion the heart rate decreased to 75 beats per minute.

Side effects. No serious side effects were observed. A few of the patients, when asked, reported slight palpitations. A slight tremor and flush occurred in some patients but caused no discomfort. There

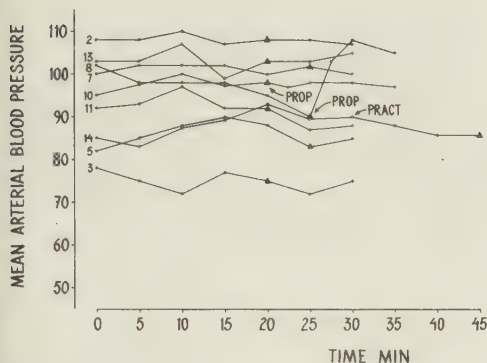


Fig. 4. Effects of TRB on maternal mean arterial blood pressure. $\blacktriangle$ denotes end of TRB infusion. Two of the patients (Nos. 8 and 10) were given propranolol (*PROP*), 1 mg. intravenously; one patient received practolol (*PRACT*), 20 mg. intravenously.

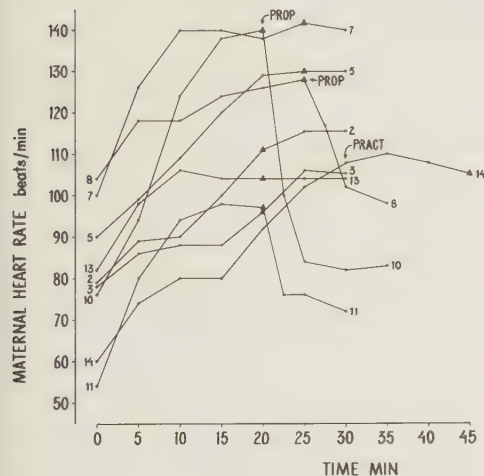


Fig. 5. Effects of TRB on maternal heart rate. Same patients as in Fig. 3. $\blacktriangle$ denotes end of TRB infusion.

were no maternal postpartum complications attributable to the TRB administration.

Effects on the fetus. Nine of the patients had a recorded increase in fetal heart rate ranging from 5 to 35 beats per minute during the infusion of TRB. The heart rate of the fetus never exceeded 160 beats per minute.

Fetal condition at birth was uniformly good; in no case was the recorded Apgar score (after 1 and 10 minutes) below 8.

Therapeutic effectiveness of intravenous terbutaline. Fig. 6 shows the effect of intravenous injection of TRB (250 μ g) in a case of oxytocin-induced uterine hyperactivity. As can be seen, there was an almost immediate decrease in basal uterine pressure and a reduction in frequency of the uterine contractions. In this patient, uterine activity was monitored for 6 hours. Despite normalization of the uterine contractions, labor did not advance satisfactorily, and a cesarean section was performed 17 hours after the injection. The child, weighing 3,240 grams, was in good condition and had a normal Apgar score.

Fig. 7 demonstrates fetal bradycardia induced by oxytocin stimulation. The patient (para 1) had a moderate pre-eclampsia and low values of estriol in urine and HCS in plasma. In the thirty-eighth week of pregnancy an oxytocin infusion (2.5 mU. per minute) was started on the presumed diagnosis of insufficiency of the placenta. After the infusion rate had been increased to 10 mU. per minute, fetal bradycardia appeared and continued despite immediate cessation of the infusion. Intravenous injection of TRB (250 μ g) rapidly decreased the frequency of the uterine contractions and also normalized the fetal heart rate. The patient was delivered by cesarean section 2 days after the oxytocin administration. The child, weighing 2,460 grams, was in good condition and had a normal Apgar score.

Comment

The mechanism behind the uterus-relaxing effect of β -receptor stimulation is not established. β -receptor stimulators have been shown to cause a cessation of spontaneous action potentials and to produce hyperpolarization of the uterine cell membrane.¹⁹ This might contribute to their relaxing action by inhibition of the electrical activity that triggers the mechanical events. However, in both rat uterus²³ and human myometrium,¹ it was demonstrated that the relaxing effect of β -receptor stimulation did not critically depend on the membrane potential, as relaxation could be obtained in a fully depolarized muscle. β -receptor stimulation increases the intracellular content of cyclic adenosine-3',5'-monophosphate (cyclic AMP) in uterine smooth muscle by effects on adenyl cyclase,²² and it has been shown that this increase can be correlated with the relaxing effect.²⁰ It is commonly accepted that the concentration of free myoplasmic calcium determines the degree of activation of the

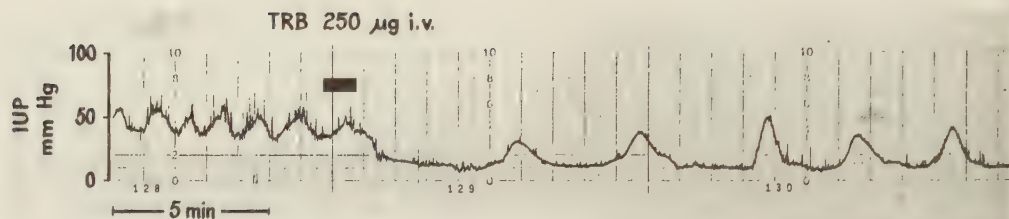


Fig. 6. Effects of TRB, 250 μ g intravenously, on uterine hyperactivity induced by oxytocin. Infusion of oxytocin was stopped a few minutes before the start of the recording. IUP = intrauterine pressure.

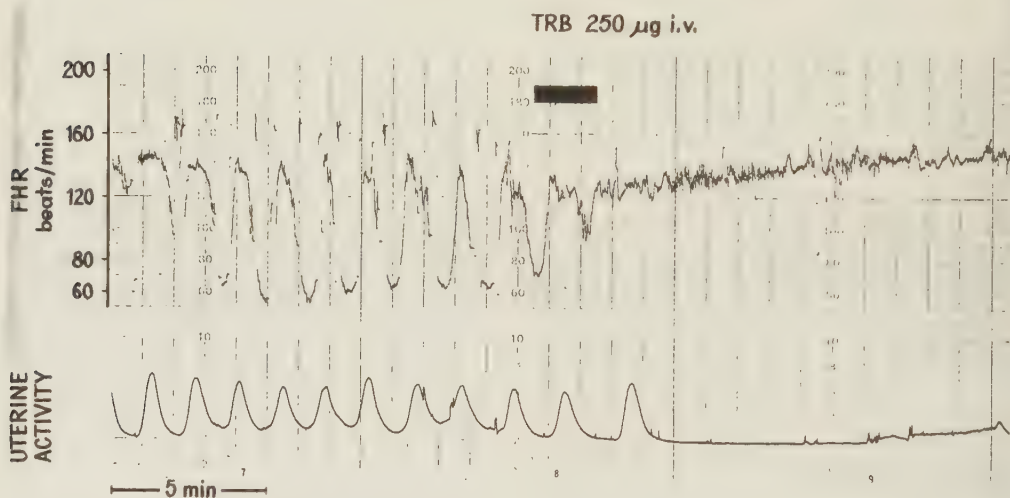


Fig. 7. Effects of TRB, 250 μ g intravenously, on uterine activity (external recording) and fetal heart rate. Fetal bradycardia developed during infusion of oxytocin. Recordings performed immediately after the oxytocin infusion had been stopped.

contractile system of a muscle cell.⁹ It has been suggested that cyclic AMP can decrease the intracellular concentration of free calcium, thereby producing muscle relaxation, by promoting active extrusion of calcium from the cell and/or by increasing the binding of calcium to intracellular structures, e.g., the sarcoplasmic reticulum.²⁰ Active, cyclic AMP-stimulated extrusion of calcium would also explain β -adrenergic-mediated hyperpolarization of the uterine cells.^{13, 20}

β -receptor stimulation involves activation of adenyl cyclase and changes in cyclic AMP content, not only in the uterus but also in other types of smooth muscle, in heart, in liver, and in fat cells.²² So far, no β -receptor stimulator is available with

effects selectively on one tissue, e.g., uterus. It is possible to separate, to a certain extent, the cardiac β -receptors mediating tachycardia and increased contractile force (β_1) from those associated with, e.g., uterine and bronchial relaxation and peripheral vasodilatation (β_2).¹⁵ All β -adrenergic agents presently in use as uterine relaxants, however, even those characterized as selective β_2 -receptor stimulators, can be expected to produce cardiovascular side effects, especially when given in high doses.

The present results show that TRB is an effective inhibitor of spontaneous and oxytocin-induced uterine activity during advanced term labor. Most of the investigated patients had a strong uterine

activity; the mean intensity was 57 mm. Hg and the mean frequency was 4.2 contractions per 10 minutes. In doses producing significant uterine inhibition, TRB produced a tolerable increase in maternal heart rate, no significant changes in maternal arterial blood pressure, and practically no subjective symptoms. In some cases a moderate increase in fetal heart rate was seen, but fetal heart rate never exceeded 160 beats per minute. There were no signs of tachyphylaxis during the infusions. An important clinical application of an effective β_2 -stimulator should be the management of abnormal uterine activity with unwanted consequences for fetus and mother. The immediate effectiveness of TRB for inhibiting unwanted uterine activity is well illustrated in the two patients in whom injudicious use of oxytocin had resulted in uterine hyperactivity (Fig. 6) and fetal bradycardia (Fig. 7), respectively.

Compared with other β -receptor stimulators, such

as isoxsuprine^{12, 17} and orciprenaline,^{4, 24, 25} TRB seems to offer the advantage of being more active on the uterine β_2 -receptors than on the cardiac β_1 -receptors, resulting in less pronounced cardiac side effects. A similar selectivity for the uterine β_2 -receptors has been demonstrated for ritodrine, a derivative of isoxsuprine,^{5, 6, 8, 11, 14} fenoterol, a derivative of orciprenaline,¹⁸ and salbutamol.¹⁶ In our experience, TRB—being widely used as a bronchodilator—seems to deserve further evaluation in respect to its ability to inhibit unwanted uterine activity. Its positive chronotropic action, although not excessive in the doses used in the present study, can be expected to be the main side effect of high doses. Probably this action not only is produced by a direct effect on the cardiac β_1 -receptors but may also, in part, be regarded as a baroreceptor-induced reflex adjustment in response to peripheral vasodilatation.³

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TERBUTALINE INHIBITION OF MIDTRIMESTER UTERINE
ACTIVITY INDUCED BY PROSTAGLANDIN $F_{2\alpha}$ AND HYPER-
TONIC SALINE

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Summary

The effect of the betareceptor stimulator, terbutaline, on uterine activity induced by intra-amniotic injection of prostaglandin $F_{2\alpha}$ or hypertonic saline was investigated in 20 patients undergoing therapeutic abortion in the second trimester. Intrauterine pressure was recorded, and the basal tonus, and the intensity, frequency, and "total" activity of the uterine contractions, expressed in Montevideo Units (M U), were measured.

Uterine activity was higher in the prostaglandin group, 393 M U (mean value), than in the hypertonic saline group, 238 M U. However, terbutaline, infused at a rate of 5 - 20 μ g/min, decreased the activity by approximately the same absolute amount in the two groups to 214 M U in the prostaglandin group and to 68 M U in the saline group. In some patients of the saline group, terbutaline completely inhibited the uterine contractions.

Basal tonus, which was high in the prostaglandin group, 28 mm Hg (mean value), decreased to 17 mm Hg during terbutaline infusion. In the saline group, basal tonus decreased from 10.5 to 7.5 mm Hg.

It is concluded that uterine activity, induced by intra-amniotic injection of prostaglandin $F_{2\alpha}$ or hypertonic saline, can be inhibited by terbutaline. The mechanisms of action of prostaglandins and hypertonic saline that induce uterine activity are discussed.

Introduction

Inhibition of uterine activity, spontaneous or evoked by various stimuli, such as oxytocin and prostaglandins, is required in many clinical situations. Here, a drug that effectively inhibits uterine activity - irrespective of its mode of induction -, has a rapid action, and minimum side effects would be of great clinical importance. Some adrenergic beta receptor stimulating agents such as ritodrine, salbutamol, and fenoterol have proved to be promising in this respect, effectively abolishing uterine activity with only moderate cardiovascular side effects (Baumgarten et al. 1971, Landesman et al. 1971, Barden 1972, Bieniarz et al. 1972, Maiss and Legerlotz 1972, Liggins and Vaughan 1973, Nochimson et al. 1974). Previous studies (Andersson et al. 1975 a, b, Ingemarsson 1975) have shown that also the beta receptor stimulator terbutaline effectively inhibits spontaneous and oxytocin-stimulated uterine activity, both at term and in premature labour, with minor effects on the circulation of mother and fetus.

However, conflicting results have been obtained concerning the effects of beta receptor stimulators on prostaglandin-induced uterine activity. Thus, it was shown that ritodrine and orciprenaline inhibited uterine activity induced by prostaglandin $F_{2\alpha}$ in humans (Lindmark et al. 1973), but also that ritodrine was ineffective in the same situation in the pregnant baboon (Wilson et al. 1974). The present study was undertaken to obtain information on the effects of terbutaline on uterine activity induced either by prostaglandins or by hypertonic saline injected into the amniotic sac, an abortifacient procedure possibly involving synthesis and release of prostaglandins (Gustavii 1973). The actions of the drug were therefore investigated in 20 patients undergoing therapeutic abortion in the second trimester.

Patients and methods

Twenty healthy patients aged 16 – 30 years (mean 22 years), weighing 52 – 90 kg (mean 62 kg), admitted to the hospital for therapeutic abortion in the 16th to 20th week of pregnancy, were investigated. The purpose of the investigation and the procedure involved were fully explained. Each patient consented verbally.

The patients were divided into two groups according to the mode of abortion-induction.

A. Prostaglandin group: ten patients, five primigravidae and five multigravidae. Four were in the 16th – 17th week of pregnancy, six in the 18th – 20th week.

B. Hypertonic saline group: ten patients, nine primigravidae and one multigravidae. Five patients were in the 16th – 17th week of pregnancy, five in the 18th – 20th week.

Experimental procedure. In the hypertonic saline group, transabdominal puncture of the uterine cavity was performed and 100 ml of amniotic fluid was withdrawn. Then 20 per cent NaCl-solution was instilled, 10 ml per week of pregnancy. In the prostaglandin group, no amniotic fluid was withdrawn, but 25 mg of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) was instilled. A catheter for epidural anaesthesia (Portex 100/380/20, open end with side holes) was introduced into the uterine cavity and connected to a pressure transducer (Hewlett Packard, 1280 B). The diaphragm of the transducer was set at the level of the symphysis. Intrauterine pressure was recorded on a cardiotocograph (Hewlett Packard, 8020 A). The intensity of uterine contraction was measured as the increase in intrauterine pressure (mm Hg) above the basal level. Frequency was expressed as the number of contractions during 10 min. Uterine activity was expressed in Montevideo Units and calculated

for each 10-min period. Maternal heart rate was monitored on the cardiotocograph by means of an ultrasonic flow detector (Hewlett Packard). Blood pressure was recorded by indirect brachial determinations every five min.

Terbutaline was infused intravenously with an infusion pump (IVAC 501, AGA Sweden) through a catheter placed in a forearm vein. Intrauterine pressure was recorded intermittently in the patients of the prostaglandin group before, and up to six h after the injection of the prostaglandin, and then continuously for 6 – 14 h. If the activity was low after six h, a second intrauterine injection of $\text{PGF}_{2\alpha}$, 25 mg, was given before administering terbutaline. This was done in three patients. After the administration of terbutaline, four patients received a second injection of $\text{PGF}_{2\alpha}$.

In those receiving hypertonic saline, intrauterine pressure was recorded intermittently before and during the first 12 – 22 h after the instillation. The pressure was then recorded continuously for 4 – 8 h.

The infusion of terbutaline was started when labour-like contractions had been recorded for at least one h. In the prostaglandin group, terbutaline was given five h (mean value; range 2 – 6 h) after the last administration of $\text{PGF}_{2\alpha}$; in the hypertonic saline group, the time between instillation of saline and terbutaline infusion averaged 24 h (range 12 – 32 h).

The terbutaline infusion was started at a rate of five $\mu\text{g}/\text{min}$ for a 10-min period. Then the infusion rate was increased by five $\mu\text{g}/\text{min}$ every 10 min until 20 $\mu\text{g}/\text{min}$ was reached. Thus a total of 500 μg of terbutaline was given for 40 min.

No patient received oxytocin. Before and during the administration of terbutaline, no analgetic was given. After that, when needed, ketobemidon (Ketogin) was given for pain relief.

Results

Fig. 1 shows the effects of terbutaline on uterine activity induced by $\text{PGF}_{2\alpha}$ and hypertonic saline. In the prostaglandin group, the uterine activity was considerably higher (mean 393 Montevideo Units) than in the hypertonic saline group (mean 238 Montevideo Units). In two of the patients of the saline group, uterine activity was abolished during the terbutaline infusion (Fig. 2).

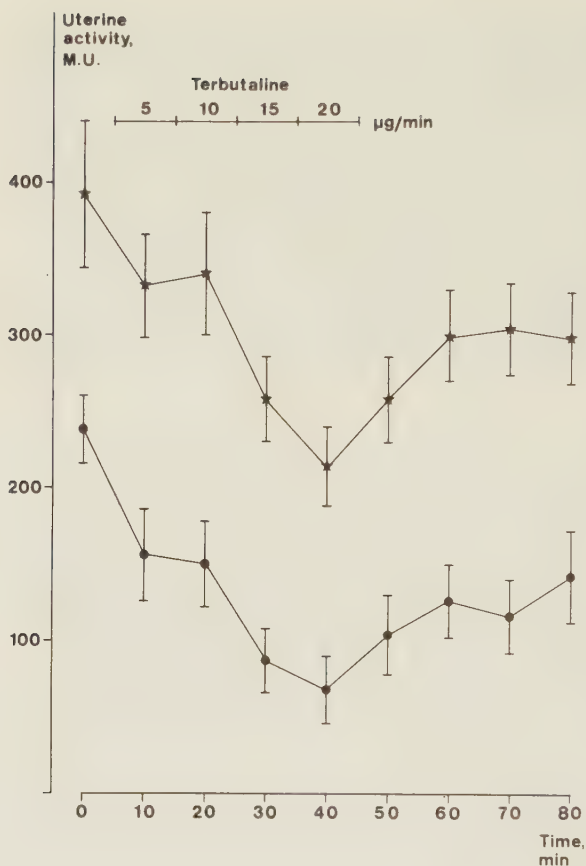
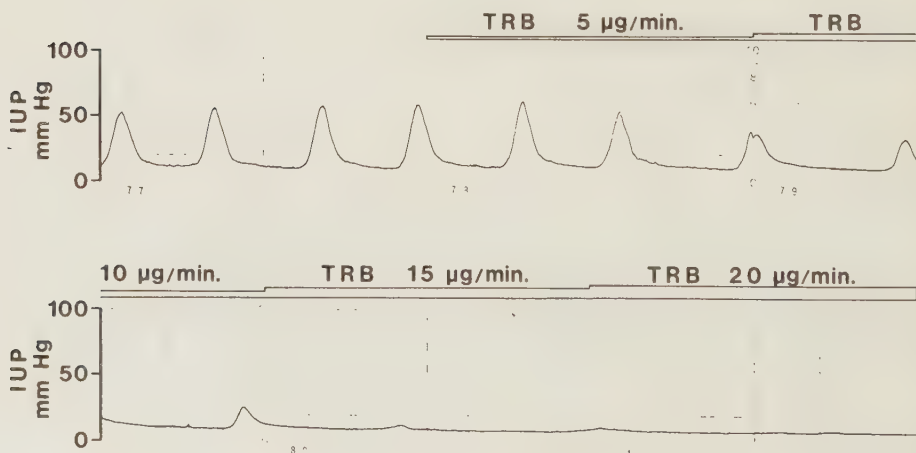


Fig. 1.

Effects of terbutaline on midtrimester uterine activity (M U) induced by intra-amniotic administration of hypertonic saline (●—●) and prostaglandin F_{2α} (*—*). Mean $\pm$ SEM (n in each group = 10).

Fig. 2.

Original record of intrauterine pressure (IUP) in one of the patients given hypertonic saline intra-amniotically. Infusion of terbutaline (TRB) effectively inhibited the uterine contractions.



The effect of the drug seemed slighter on prostaglandin induced contractions, but the activity decreased in both groups by approximately the same absolute amount: 179 Montevideo Units in the prostaglandin group; 170 Montevideo Units in the hypertonic saline group.

The frequency of the uterine contractions was diminished in the prostaglandin group from 8.0 to 5.3, and in the saline group from 4.8 to 1.9 contractions/10 min (Fig. 3).

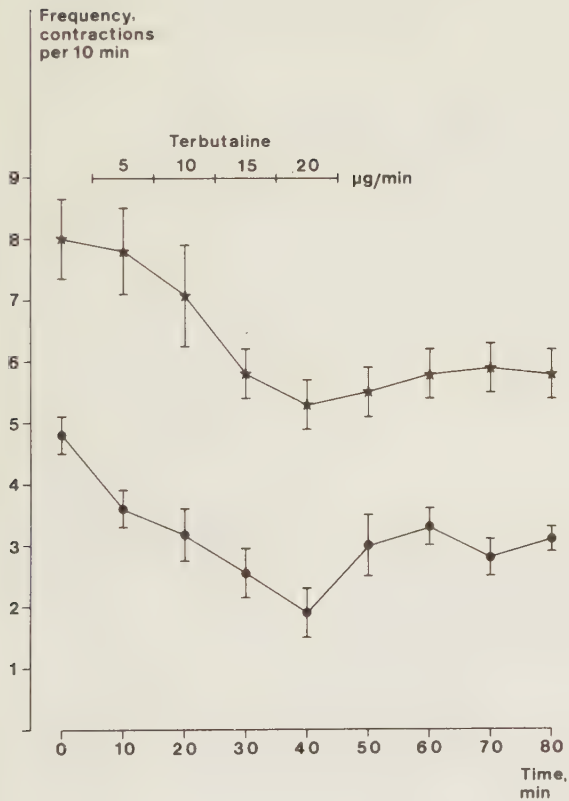


Fig. 3.

Effects of terbutaline on uterine contraction frequency (contractions/10 min) after intra-amniotic administration of hypertonic saline and prostaglandin $F_{2\alpha}$. Symbols as in Fig. 1.

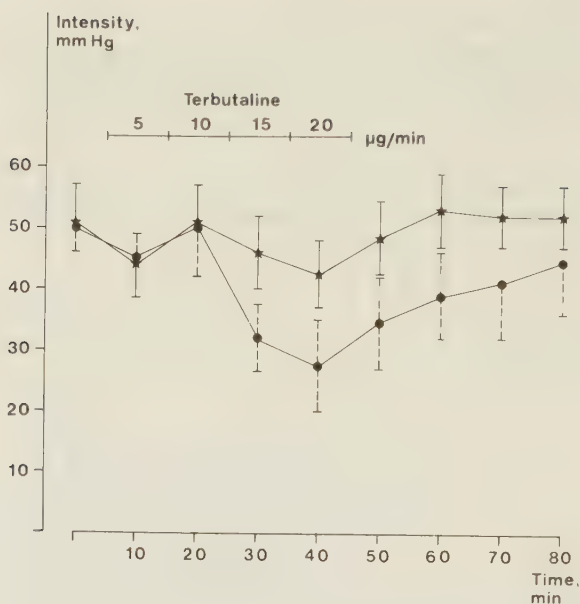


Fig. 4.

Effects of terbutaline on the intensity of uterine contractions induced by intra-amniotic administration of hypertonic saline and prostaglandin $F_{2\alpha}$. Symbols as in Fig. 1.

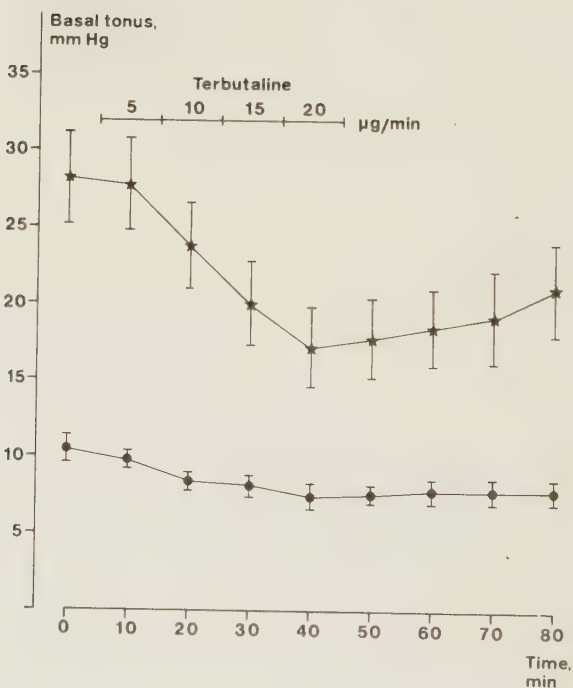


Fig. 5.

Effects of terbutaline on intrauterine basal tonus (mm Hg) after intra-amniotic administration of hypertonic saline and prostaglandin $F_{2\alpha}$. Symbols as in Fig. 1.

The intensity of the uterine contractions (Fig. 4) was similar in both groups at the start of the terbutaline infusion, approximately 50 mm Hg (mean value). In the prostaglandin group, the effect of the β -receptor stimulator on this parameter was slight; in the saline group, there was a decrease to a minimum of 24 mm Hg.

Basal tonus (Fig. 5) was higher among the patients given $\text{PGF}_{2\alpha}$ (mean 28 mm Hg) than among those given hypertonic saline (mean 10.5 mm Hg). In the prostaglandin group, terbutaline produced a decrease in basal tonus to a minimum of 17 mm Hg (mean value). In the saline group, the relaxing effect was slight and basal tonus decreased on average to a minimum of 7.5 mm Hg.

During the terbutaline infusion, an increase in maternal heart rate from a mean of 78 beats/min (range 60 – 92 beats/min) to a mean maximum of 115 beats/min (range 82 – 136 beats/min) was recorded. There were no significant changes in maternal blood pressure.

Three patients aborted on the initial injection of $\text{PGF}_{2\alpha}$; seven required a second injection. The mean abortion time for nine of them was 25 h (range 12 – 52 h). One patient, who had received two injections of $\text{PGF}_{2\alpha}$, had a weak uterine activity after 48 h. A third injection was given; she aborted 83 h after the first administration of the prostaglandin. One patient in the saline group had weak uterine activity after 48 h. A second injection of saline was given. She aborted 109 h after the first instillation. In the other nine patients, the mean abortion time was 41 h (range 30 – 56 h).

Discussion

The present results clearly show that terbutaline inhibits uterine activity induced by intra-amniotic injection of either hypertonic saline or $\text{PGF}_{2\alpha}$. The inhibiting effect of terbutaline on hypertonic saline-induced activity was pronounced; in some cases the uterine contractions were abolished. Both the frequency and the intensity were reduced, but the effect on basal tonus was slight, probably owing to the low basal tonus at the start of the terbutaline infusion. The mechanism by which hypertonic saline induces abortion is not clear, and several hypotheses have been advanced (for review, see Gustavii 1973). It has been suggested (Gustavii 1973) that one factor involved in the action of intrauterine hypertonic saline is the synthesis and release of prostaglandins from damaged decidual cells. The finding that the inhibitors of prostaglandin synthesis, aspirin and indomethacin, prolonged instillation/abortion time (Waltman et al. 1973) supports this. If prostaglandins are involved, betareceptor stimulation could be

expected to inhibit also uterine activity induced by exogenous prostaglandins.

Previous studies in man and baboon of the effect of betareceptor stimulators on prostaglandin-induced uterine activity have given somewhat conflicting results. In women undergoing therapeutic abortion in the second trimester of pregnancy, Lindmark et al. (1973) found that the betareceptor stimulators orciprenaline and ritodrine effectively inhibited uterine motility induced by intra-amniotic injection of $\text{PGF}_{2\alpha}$. Baillie and Jonathan (1972) and Scher and Baillie (1972) reported that orciprenaline inhibited uterine activity induced by intravenously given $\text{PGF}_{2\alpha}$ at term. The drug was much more effective, however, on activity induced by oxytocin. In the pregnant baboon, on the other hand, the betareceptor stimulators isoprenaline, orciprenaline, and ritodrine were all found to be ineffective for inhibition of $\text{PGF}_{2\alpha}$ -induced activity; in some cases, they even increased the activity (Wilson et al. 1974).

The present results and those of Lindmark et al. (1973) and Scher and Baillie (1972) suggest that betareceptor stimulators in man are able to exert an inhibiting effect on uterine activity induced by $\text{PGF}_{2\alpha}$, both at the second trimester of pregnancy and at term. The cause of the ineffectiveness of these drugs in the pregnant baboon is unclear but may be due to species differences.

In the present patients, the inhibiting effect of terbutaline on $\text{PGF}_{2\alpha}$ -induced activity was moderate compared with its effect on hypertonic saline-induced activity. On the other hand, the inhibition in absolute terms (Montevideo Units) was similar, and the lower effectiveness on $\text{PGF}_{2\alpha}$ -induced activity might therefore be due to the uterine activity being higher in the prostaglandin group. However, the activities induced by the two agents showed certain differences. The prostaglandin induced activity had a higher contraction frequency and a higher basal tonus than that induced by saline. Labour induced by prostaglandins during the first 24 h is often complicated by an increase in uterine basal tonus and abnormal contraction patterns (Bygdeman et al. 1968, Roth-Brandel 1970, Roberts and Turnbull 1971).

Clegg et al. (1966) proposed a double mechanism for the prostaglandin-induced uterine stimulation: in low concentrations, prostaglandins enhance the response to other stimuli, possibly by facilitation of excitation-contraction coupling; in high concentration, they have a "direct" effect on the cell membrane, resulting in depolarization of the myometrial cells. The response of the human uterus to prostaglandins could be a combination of these two effects, and the difference between activity induced by hypertonic saline (via prostaglandins) and intra-amniotically injected prostaglandins could depend on what effect predominated.

In vitro experiments on isolated human myometrium suggest that the relaxing effect of betareceptor stimulators on strips contracted by prostaglandins is slight (Andersson et al. 1975 c). It should be noted, however, that in the present patients the increase in basal tonus produced by $\text{PGF}_{2\alpha}$, which can possibly be attributed to a "direct" effect, was reduced by terbutaline.

Previous studies (Andersson et al. 1973, 1975 a, b, Ingemarsson 1975) have shown that terbutaline is capable of inhibiting uterine activity both in vitro and in vivo. Thus terbutaline inhibited both spontaneous and oxytocin-induced activity at term, and also premature labour. These observations, together with the present findings, therefore suggest that uterine activity evoked by different stimuli, including prostaglandins, can be inhibited by beta-receptor stimulation. It has been much discussed whether the myometrial inactivity in human pregnancy is due to a lack of stimulating factors (e.g., oxytocin, prostaglandins) or to an action of some "blocking" substances, which decrease or disappear before the onset of labour (e.g., progesterone; see review by Bengtsson 1973). It cannot be excluded that β -receptor stimulation is of importance in this connexion, being a part of the mechanisms securing the maintenance of pregnancy.

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EFFECT OF TERBUTALINE ON PREMATURE LABOUR -
A DOUBLE-BLIND PLACEBO-CONTROLLED STUDY

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Abstract

The effect of terbutaline, a "selective" β_2 -receptor stimulator, was compared with that of placebo in 30 patients in premature labour. Treatment consisted of an intravenous infusion for at least 8 hours, and then of subcutaneous injections 4 times daily for 3 days together with peroral treatment, which was continued until the end of the 36th week of pregnancy.

In 12 of 15 terbutaline-treated patients (80 per cent) premature labour was arrested beyond the treatment period, compared with 3 of 15 in the placebo group (20 per cent). This difference is statistically significant ($p < 0.01$).

No serious side effects were observed. During infusion, there was an increase in maternal heart rate. This was more pronounced in the terbutaline group (30 per cent) than in the placebo group (9 per cent). There were no adverse effects on blood pressure, but fetal tachycardia was observed more frequently in the terbutaline than in the placebo group. The results suggest that terbutaline is a safe, potent, and well-tolerated inhibitor of premature labour.

Introduction

Many drugs have been tested with varying degrees of success in order to inhibit uterine activity in premature labour (for review, see Zuspan et al. 1972) (1). Beta-adrenergic receptor stimulating compounds have been used for several years; at present, these drugs seem to offer a promising alternative in the therapy. The first drug of this type used clinically was isoxsuprine. This was shown to depress uterine activity both at term (2, 3, 4) and in premature labour (5, 6, 7). Unfortunately, the cardiovascular side effects reduced its clinical usefulness. The same problem has been reported by investigators using orciprenaline (8, 9, 10).

Drugs have since become available that have a relatively selective stimulatory effect on the beta-receptors (β_2) of the uterus and only to a minor degree on the beta-receptors (β_1) of the heart. These agents effectively suppress uterine contractions without adverse effects on the circulation. Drugs of this type, recommended for therapy of premature labour, are ritodrine (11, 12, 13, 14), fenoterol (15), and salbutamol (16, 17).

The extent that these drugs are able to postpone delivery at premature labour is often questioned, as it is difficult to establish this diagnosis accurately. It is also difficult to estimate

the effect of conservative treatment, e.g., sedation and bed rest. To settle this matter, adequately controlled investigations are necessary (18). Unfortunately, this type of study has seldom been performed.

Terbutaline, a β -receptor stimulator with effects mainly on β_2 -receptors (19), was previously shown to effectively inhibit myometrial activity at term, both *in vitro* (20, 21) and *in vivo* (21, 22). The present investigation evaluated the effect of terbutaline on premature labour in a double-blind, placebo-controlled study.

Patients and methods

To obtain comparable groups of patients, only those with premature labour of unknown aetiology were investigated. Those with toxæmia, uterine malformations, fever, ruptured membranes, twins, or vaginal bleedings were excluded.

Patients fulfilling the following criteria were accepted:

1. Duration of gestation 28 – 36 weeks.
2. Intact membranes.
3. Painful, regular uterine contractions, occurring at intervals of less than 10 minutes, recorded for at least 30 min by external tocography.
4. The cervix effaced or almost effaced, dilated at least 1 – 2 cm, but not more than 4 cm.

All patients were examined by the same investigator. They were informed about the aim of the investigation and that a new drug was to be tested that could produce side effects such as tachycardia and palpitation. Uterine contractions were recorded by means of external tocography (Hewlett Packard model 1280 B). During infusion therapy, blood pressure was followed by indirect brachial pressure determinations every 10 minutes. The pulse frequency was recorded simultaneously. Fetal heart rate was monitored on the cardiotocograph with an ultrasonic flow detector (Hewlett Packard). Terbutaline and placebo (= physiologic saline) were infused intravenously by means of an infusion pump (IVAC 501, AGA, Sweden).

All patients selected for the investigation were treated with bed rest and sedation. In addition, terbutaline or placebo were allocated at random. The two groups were treated in a double-blind manner.

Once selected for treatment, the patient received 10 mg diazepam i.m. If there was no obvious effect on the uterine contractions,

treatment was continued with infusion of terbutaline or placebo in 5 per cent glucose solution for at least 8 hours. The initial infusion rate was 40 drops/min, corresponding to 10 $\mu\text{g}/\text{min}$ of terbutaline. At 10-min intervals, the infusion rate was increased by 20 drops/min until 100 drops/min, corresponding to 25 $\mu\text{g}/\text{min}$ of terbutaline, was reached or until the uterine activity had ceased. When this was attained, the infusion rate was maintained for one hour. It was then decreased gradually by 5 $\mu\text{g}/\text{min}$ at intervals of 30 minutes until the lowest effective maintenance dosage was reached. The infusion was stopped after 8 hours, provided the uterine activity had completely ceased. Otherwise, the infusion was continued until either this occurred or until it was obvious that the treatment had failed.

If infusion with 100 drops/min had no effect during one hour, the infusion rate was lowered to 20 drops/min as a maintenance dose. This ensured that the patients in the placebo group did not get more fluid intravenously than the patients in the terbutaline group. Bed rest was prescribed and subcutaneous injections (corresponding to 250 μg of terbutaline) were administered 4 times daily for 3 days. Simultaneously, oral treatment (corresponding to 5 mg $\times$ 3 of terbutaline) was started and continued to the end of the 36th week. The patients were then mobilized and sent home without further treatment. If uterine activity recurred during the treatment period, a new sequence of infusions and subcutaneous injections was begun.

30 patients, 15 in the terbutaline group and 15 in the placebo group, were selected for the study. The investigation began on 1 February 1973 and ended on 1 November 1974. During this period, 6,304 children were delivered; 323 of them weighed less than 2,500 g (5.1 per cent).

Table I. Comparison of the terbutaline with the placebo group (mean $\pm$ S.E.M.). The differences between the various parameters are statistically not significant.

	Maternal age, years	Gravidity	Parity	Cervical dilatation, cm	Duration of pregnancy on presentation, days
Terbutaline group	26.4 $\pm$ 1.1	2.0 $\pm$ 0.3	0.6 $\pm$ 0.2	2.2 $\pm$ 0.2	228 $\pm$ 3.7
Placebo group	24.1 $\pm$ 1.5	2.2 $\pm$ 0.3	0.6 $\pm$ 0.3	2.3 $\pm$ 0.2	229 $\pm$ 4.0

Table I shows the clinical data on the terbutaline and the placebo groups. Both are statistically comparable. Patients with delivery postponed until the 37th week of gestation or later were considered successfully treated; all others, failures. Calculations of the number of days the premature labour had been arrested were not considered meaningful, as the patients entered the trial at different times of gestational age and all treatment was stopped at the end of the 36th week.

Statistical evaluation

Student's t-test was used for statistical comparison of the different parameters in the terbutaline and placebo groups (Table I). A chisquare test was used to compare the results of the treatment in the terbutaline and the placebo groups (Table II).

Table II. Results of treatment.
Del. = delivery. Prem. = premature

	Del.during the initial infusion	Arrested 1-7 days but prem. del.	Arrested 8-15 days but prem. del.	Arrested beyond the 36th week	Total number of patients
Terbu- taline group	0	2	1	12	15
Place- bo group	10	1	1	3	15

Results

Table II shows the results of the treatment. Premature labour was arrested beyond the treatment period in 12 of 15 (80 per cent) of the patients receiving terbutaline and in 3 of 15 (20 per cent) in the placebo group. The difference between the two groups is statistically significant ($p < 0.01$).

In the placebo group, 10 patients were delivered within 24 hours from the start of infusion. In two, premature labour was arrested for 3 and 14 days, respectively. They were delivered prematurely in the 31st and the 34th gestational week, respectively. Three patients were delivered at term.

In the terbutaline group, premature labour was arrested beyond the treatment period in 12 patients. Five of them returned to the hospital within a few days and were delivered in the 37th week. Two were delivered in the 38th week and the rest at term. There were three failures in the terbutaline group. In one patient, in the 29th week of pregnancy, premature labour could not be arrested for more than 48 hours, despite intermittent infusion therapy (total infusion time 27 hours). During the end of the treatment, she showed vaginal bleeding, and the infusion of terbutaline was stopped on suspicion of abruptio placenta. This was confirmed after delivery when the placenta was investigated and was the probable cause of the failure. In two patients with the cervix dilated 3 cm, the delivery could be delayed only 2 and 15 days, respectively. They were delivered in the 34th and 35th week, respectively.

Table III. The results in the terbutaline group related to infusion rate and number of infusions

No. of patients	No. of infusions	Maximal infusion rate $\mu\text{g}/\text{min}$	Total dosage (mean and range)	Successful	Unsuccessful
8	1	10	1800 (1650-1950)	8	0
1	1	15	2150	1	0
1	1	20	3000	1	0
1	2	15	3000	0	1
1	3	15	10400	0	1
1	4	25	14900	0	1
1	5	25	41500	1	0
1	8	25	25900	1	0
15				12	3

Table III shows that the dosage of terbutaline needed to inhibit the uterine activity varied. It also shows that one infusion and the initial infusion rate ($10 \mu\text{g}/\text{min}$) was sufficient in 8 patients. On the other hand, one patient in the 31st week of pregnancy with strong uterine activity needed 8 infusions (total dosage $25.900 \mu\text{g}$ of terbutaline) during the first 10 days after arriving at the hospital. No further infusion was needed thereafter and delivery occurred in the 37th week.

The condition of the children at delivery was usually good. In the placebo group, 3 children had an Apgar score less than 8 after 1 min, and it remained below 8 for 2 of them after 10 min. In the terbutaline group, 2 children had an Apgar score less than 8 after 1 min, and all had a full Apgar score after 10 min. In the placebo group, 10 children weighed less than 2.500 g, compared with 4 in the terbutaline group. The mean birth weight was 2.190 and 3.060 g, respectively. All children survived, and all the pre-matures could be sent home after treatment at the paediatric ward for varying times.

Side effects of the treatment were common but not serious. Maternal tachycardia was seen in every case during infusion of terbutaline. The placebo group experienced a similar side effect, but to a lesser degree. The mean pulse rate increased from 90 to 120 (30 per cent) during the initial infusion of terbutaline and from 86 to 94 (9 per cent) in the placebo group (Table IV).

Table IV. Maternal heart rate before and during the initial intravenous infusion of terbutaline or placebo (mean $\pm$ S.E.M.)

	Mean maximum maternal heart rate (beats/min)	
	Before treatment	During intravenous infusion
Terbutaline group	90.1 $\pm$ 2.2	120.1 $\pm$ 4.2
Placebo group	86.1 $\pm$ 2.7	94.4 $\pm$ 1.8

Decrease in systolic blood pressure exceeding 20 mm Hg occurred once in the terbutaline group and twice in the placebo group, but was symptomless. The systolic blood pressure returned to normal after reducing the infusion rate for a short time or after changing the patients position.

Fetal tachycardia often accompanied maternal tachycardia during terbutaline infusion; in 80 per cent of the cases, the fetal heart rate reached or exceeded 150 beats/min. This occurred in 30 per cent of the cases in the placebo group. However, in no case did the fetal heart rate exceed 175 beats/min.

Side effects did not lead to any discontinuance of treatment. During oral treatment with terbutaline, a slight tremor was often observed, but was well tolerated.

Comment

The obstetrician encounters big problems in establishing the diagnosis of premature labour, as opposed to "false" labour. Consequently, it is difficult to assess the efficacy of treatment methods, and the importance of controlled trials has been stressed in the discussion of treatment of premature labour (18). This type of investigation finally demonstrated that progesterone was ineffective in the treatment of threatened abortion and premature labour (23, 24).

Many authors during the past five years have reported promising results from treatment of premature labour with "selective" β -receptor stimulating agents, but only a few of these studies have been adequately controlled. Ritodrine was investigated by Sivasamboo (25) in a randomized comparison with chlordiazepoxide in 65 patients in premature labour. Significantly better results were achieved in the ritodrine group (effective in 70 per cent of the patients) than in the chlordiazepoxide group (41 per cent). Ritodrine was also investigated by Wesselius-de Casparis et al. (11) in a double-blind placebo-controlled multicentre trial: 68 patients in premature labour with intact membranes were studied. The pregnancy could be prolonged beyond the treatment period (7 days) in 77 per cent of those receiving ritodrine compared with 52 per cent of those on placebo. However, it is well known that the results of treatment of premature labour with different drugs largely depend on the selection criteria and even on the individual clinician. In this multicentre trial, several investigators selected the patients; this might explain the relatively high degree of success in the placebo group.

In the present study, all patients were examined by the same investigator in order to minimize this problem. The patients were selected according to the recommendations by Zuspan et al. (1). Even if it is impossible to diagnose premature labour for certain, considerable accuracy can be achieved by using the means at present available. In this study, external tocography has been performed in all patients for at least 30 min before the start of any treatment. This method allows the duration, frequency, and relative intensity of the contractions to be studied even if it is impossible to quantitate the intensity accurately. Regular, frequent contractions during this observation period, together with a cervical status too advanced for the time of gestation, or progressive dilatation and/or effacement of the cervix, have been regarded as signs of premature labour. However, if this observation period is too prolonged, a critical point can be reached where treatment by any drug will fail. This is illustrated by a patient in the terbutaline group who only after several hours of observation could be accepted for the trial. The cervix at that time was effaced and dilated 3 cm. The premature labour

could be arrested for only 2 days, despite infusion treatment during most of this period.

A successful result depends on individual dosage and an intensive therapy. This requires a drug that can be tolerated by the patients, despite long infusion time and repeated infusions. This study indicates that the side effects of terbutaline therapy are minor and that terbutaline is well suited for this type of intensive therapy. A comparison of terbutaline's side effects with those of other drugs of this type - e.g., ritodrine, fenoterol, and salbutamol - is difficult to make, as selection criteria, duration of treatment, and dosage schedule are different in presented studies. However, the reported side effects on the maternal circulation of these drugs (11, 12, 13, 14, 15, 16, 17, 26) seem to equal the circulatory effects of terbutaline treatment.

The results of the present study indicate that terbutaline is a potent and safe inhibitor of premature labour. In the terbutaline group, premature labour could be arrested beyond the treatment period in 80 per cent of the patients compared with 20 per cent in the placebo group. This last figure represents the effect of conservative and placebo treatment and/or misdiagnosed patients. It is reasonable to believe that the conservative treatment has some effect on premature labour, thus suggesting that the number of misdiagnoses is low, and consequently, that the selection criteria used in this study are adequate.

There was no perinatal or neonatal mortality among the children in this material. However, the fact that only 4 children in this group weighed less than 2.500 g compared with 10 children in the placebo group and that the mean birth weights were 3.060 and 2.190 g, respectively, demonstrate the value of terbutaline treatment. A long-time follow-up of the children was not considered meaningful in this small series. Such investigations and further evaluation of the treatment scheme and the different components of the therapy are necessary to establish the best way to use terbutaline in premature labour.

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